Nouveaux outils et optimisation des outils existants pour la réhabilitation respiratoire et la ré-autonomisation des patients atteints d'un handicap ventilatoire.

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THÈSE

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Nouveaux outils et optimisation des outils existants pour la réhabilitation respiratoire et la ré-autonomisation des patients atteints de handicap ventilatoire

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Liste des publications au cours de la thèse

En lien avec le sujet de thèse :

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Bonnevie T, Prieur G, Gravier FE, Combret Y, Médrinal C. Kinésithérapie et syndrome ventilatoire obstructif, en phase stable. EMC - KINESITHERAPIE-MEDECINE PHYSIQUE-READAPTATION. 2019.

Nouveaux outils et optimisation des outils existants pour la réhabilitation respiratoire et la ré-autonomisation des patients atteints de handicap ventilatoire

Table des matières

Introduction générale

Le sport, c'est la santé ! Tel est le message délivré par le Ministère des Solidarités et de la Santé ainsi que par le Ministère des Sports depuis plusieurs années, ayant récemment conduit à la Stratégie Nationale SPORT SANTE 2019-2024 (1). Ce plan national vise à lutter contre l'inactivité physique, facteur indépendant de mortalité (2, 3) responsable de 6% des décès à l'échelle mondiale (quatrième cause de mortalité) (4). L'inactivité physique est associée à un poids économique majeur (environ 54 milliards de dollars au niveau international en 2013) (5). Elle est également responsable d'une augmentation du risque de mortalité dans de nombreuses pathologies chroniques (hypertension artérielle, diabète, hypercholestérolémie, obésité, pathologies cardiovasculaires), dont les pathologies respiratoires (2, 6).

Parmi les principales pathologies respiratoires, la bronchopneumopathie chronique obstructive (BPCO) est une maladie fréquente, qui peut être prévenue et traitée, caractérisée par la persistance de symptômes respiratoires (dont la dyspnée, la toux, les expectorations) en association avec une limitation ventilatoire obstructive, permanente et progressive, des voies aériennes (7). Elle est dûe par une inflammation chronique des différentes structures de l'arbre aérien. Sa cause la plus fréquente dans les pays développés est le tabagisme chronique (8), auquel s'associe l'emploi de la biomasse dans les pays en voie de développement. La BPCO figure parmi les premières causes de mortalité dans le monde (9, 10). Sa prévalence est estimée à environ 10% des adultes âgés de plus de 40 ans (11) et devrait continuer à augmenter dans les deux prochaines décennies (12). On estime ainsi que 328 millions de personnes souffrent de cette pathologie dans le monde (13). Chez certains patients, l'évolution se fait progressivement vers l'insuffisance respiratoire : hypoxémie chronique, associée ou non à une hypercapnie au cours du sommeil puis sur la totalité du nycthémère (8, 14), émaillée d'épisodes d'exacerbations dont les formes les plus sévères sont une insuffisance respiratoire aiguë hypercapnique avec

une mortalité élevée, immédiate et au décours. Bien que la BPCO soit une pathologie respiratoire, la fumée de tabac, l'hypoxémie et l'inflammation chronique entrainent également de nombreuses conséquences systémiques parmi lesquelles figurent les comorbidités cardiovasculaires, l'anémie, l'ostéoporose, l'anxiété-dépression, une dysfonction neuro-cognitive et une dysfonction musculaire périphérique (15, 16).

L'un des symptômes à l'origine du handicap ventilatoire dans la BPCO est la dyspnée. Celle-ci entraine progressivement l'éviction de l'activité physique, elle-même responsable d'un déconditionnement musculaire, créant ainsi les conditions d'un cercle d'auto-aggravation de la dyspnée (17). L'atteinte des muscles locomoteurs (perte de masse et de force musculaire, modification de la distribution des fibres musculaires en faveur des fibres glycolytiques, diminution de la capillarisation et dysfonction mitochondriale (18-25)) ne peut être expliquée uniquement par le déconditionnement musculaire. L'inflammation systématique et le stress oxydatif (26, 27), la dysfonction liée à la ventilation (28), les systèmes hormonaux et nutritifs (29, 30), le recours aux corticostéroïdes (31) ainsi que l'inhibition centrale (32) sont autant d'explications possibles. La question de la fonction musculaire est primordiale dans l'évaluation pronostique et la prise en charge des patients atteints de BPCO dans la mesure où l'altération musculaire squelettique entraîne un recours élevé au système de soins (33, 34), altère la qualité de vie et diminue l'espérance de vie, indépendamment de l'atteinte pulmonaire elle-même (35, 36).

Afin d'améliorer la dyspnée des patients, leur fonction musculaire et de rompre avec la spirale du déconditionnement, la réhabilitation respiratoire est recommandée par toutes les sociétés savantes internationales dont l'*European Respiratory Society*, l'*American Thoracic Society*, la *British Thoracic Society* et la Société de Pneumologie de Langue Française (SPLF),

qui établissent une recommandation forte (G1+ selon la classification *Grading of Recommendations Assessment, Development and Evaluation* (GRADE)) pour les patients atteints de BPCO (8, 37-39). Cela a conduit la Haute Autorité de Santé a intégrer les techniques d'amélioration de la fonction musculaire au sein du parcours de soins des patients atteints de BPCO et à généraliser leur emploi pour l'optimisation des soins. La réhabilitation respiratoire est définie par la SPLF comme « un ensemble de moyens proposés au patient atteint d'une maladie respiratoire chronique pour réduire le handicap et améliorer la qualité de vie ». Son objectif est de « maintenir dans la durée un niveau d'activité physique quotidienne jugé nécessaire à la santé physique et psychique du patient, de façon à diminuer les conséquences systémiques de la maladie et les coûts de santé » (8). La réhabilitation respiratoire est une prise en charge transdisciplinaire et associe un réentrainement à un exercice individualisé comprenant un entrainement en endurance et du renforcement musculaire périphérique, une éducation thérapeutique, une kinésithérapie respiratoire, un sevrage tabagique, un soutien nutritionnel ainsi qu'une prise en charge psycho-sociale (8, 37). De nombreuses données scientifiques supportent l'efficacité de la réhabilitation respiratoire pour améliorer la dyspnée, la fatigue, le contrôle émotionnel, la fonction musculaire, la capacité à l'exercice ainsi que la qualité de vie des patients atteints de BPCO (40-42). De plus, la réhabilitation respiratoire pourrait réduire le risque de survenue d'une exacerbation (43-45) ainsi que le risque de mortalité suivant une hospitalisation pour exacerbation (45, 46).

En pratique, l'organisation d'un programme de réhabilitation respiratoire se déroule selon trois étapes indispensables : évaluation clinique et physiologique préalable, programme initial et programme de maintien sur le long terme (8).

L'évaluation préalable est un prérequis à tout programme de réhabilitation. Elle contribue à prendre en compte les besoins du patient dans sa globalité en intégrant le caractère « systémique » de la maladie BPCO. Elle permet entre autres :

- L'évaluation à l'effort dont l'objectif est triple :
    - Écarter les contre-indications cardiovasculaires au réentrainement via un électrocardiogramme d'effort (8) ;
    - Quantifier la part des limitations ventilatoire, cardiovasculaire et musculaire à l'effort ;
    - Titrer l'intensité du réentrainement en endurance et du renforcement musculaire qui seront proposés au cours du programme de réhabilitation (8).

A cette étape, les travaux de recherche à envisager doivent, à notre avis, être orientés vers l'identification de techniques d'évaluation plus simples afin de faciliter l'accès à la réhabilitation respiratoire. Ce thème sera abordé dans la première partie de cette thèse.

Le programme initial de réhabilitation se déroule habituellement sur 4 à 10 semaines et comprend 12 à 30 séances de réentrainement à l'exercice (entrainement en endurance, renforcement musculaire, éducation thérapeutique etc.) à raison de 2 à 5 séances par semaine (8, 37, 38). Bien que différentes modalités d'entrainement soient décrites dans la littérature (travail en continu ou par intervalle, exercice à faible ou haute intensité etc.), aucune ne semble avoir clairement démontré sa supériorité (47). Par ailleurs, le nombre limité de centres de réhabilitation respiratoire (48-50) nécessite une réflexion sur de nouvelles modalités de réalisation de ces programmes de réhabilitation.

Dans ce contexte, il existe de nombreuses pistes de recherche visant :

- A délocaliser la réhabilitation hors des centres, tout en explorant les freins potentiels à cette délocalisation, dont l'altération des fonctions cognitives ;

- Optimiser les outils existants ou évaluer de nouveaux outils (définis comme des adjuvants à la réhabilitation respiratoire) qui pourraient être utilisés au cours, ou en parallèle des séances d'entrainement, afin d'en potentialiser les bénéfices.

Ces pistes seront respectivement abordées dans la première partie et la seconde partie de cette thèse.

Enfin, le programme de maintien des acquis sur le long terme devrait perdurer le plus longtemps possible. Il concerne à la fois l'activité physique mais également l'ensemble des autres comportements (abstinence tabagique, alimentation, traitements phramacologiques et non pharmacologiques, etc.). En son absence, les bénéfices obtenus lors du programme initial sont en général perdus après une année (51). Il est donc nécessaire d'accompagner le patient à travers les différentes étapes de changement des comportements, et ce dès le début du programme initial afin d'intégrer l'activité physique dans le quotidien. Il est recommandé de poursuivre une activité physique à raison de 30 à 45 minutes au moins 3 fois par semaine (8). Malheureusement, aucune donnée probante ne permet actuellement de montrer l'efficacité d'une approche spécifique et de nombreuses pistes de recherche restent ainsi à explorer. Ce thème sera abordé dans la troisième partie de cette thèse.

Ainsi, ces trois étapes (évaluation clinique et physiologique préalable, programme initial et programme de maintien sur le long terme) sont primordiales au bon déroulement et à l'efficacité des programmes de réhabilitation respiratoire. Néanmoins, chacune d'elle s'accompagne de nombreuses problématiques, incluant l'accès limité aux structures d'évaluation et de réentrainement, l'optimisation du programme d'entrainement à l'exercice ainsi que le maintien des bénéfices sur le long terme. Ces problématiques pourraient trouver

des réponses dans l'optimisation d'outils existants ou l'utilisation de nouveaux outils qui font l'objet de notre travail actuel (**Figure 1)**.

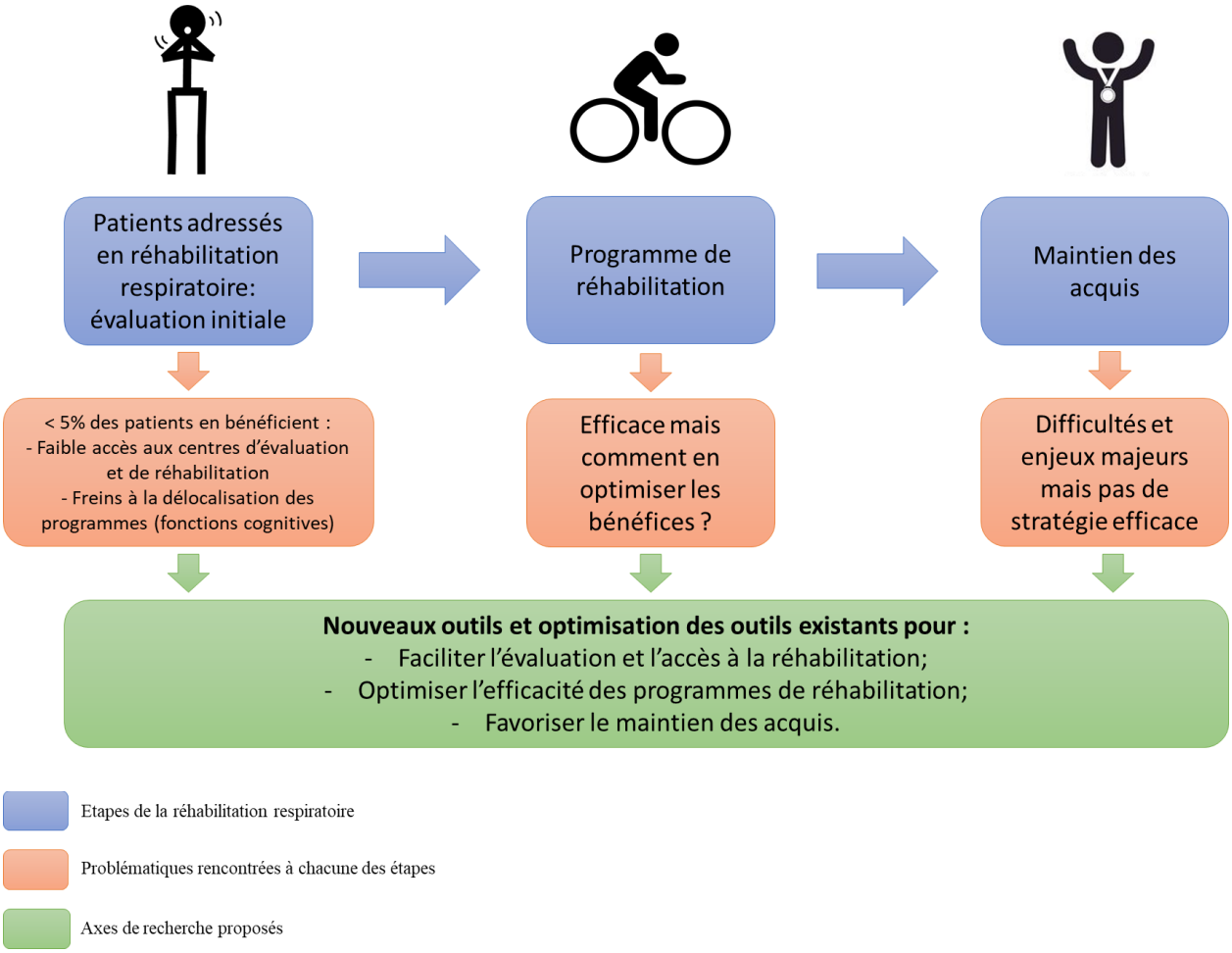

Figure 1 : *Problématiques rencontrées à chacune des étapes de la réhabilitation respiratoire et pistes de recherche proposées.*

Dans le cadre de cette thèse, nous avons cherché à explorer la façon dont de nouveaux outils ou des outils existants pouvaient être optimisés pour faciliter l'accès aux programmes de réhabilitation respiratoire, en potentialiser l'efficacité et envisager le maintien sur le long terme.

Cette thèse s'oriente donc autour de trois parties principales. La première tente de répondre à la problématique de l'accès limité aux structures d'évaluation et aux programmes

de réhabilitation respiratoire en proposant des outils permettant d'externaliser l'évaluation et la réhabilitation. Les objectifs étaient d'étudier de nouveaux outils, plus simples à utiliser en routine, pour prescrire le réentrainement à l'exercice ainsi que d'évaluer la faisabilité, la validité et l'acceptabilité d'un outil de télé-monitorage qui permettrait d'optimiser un programme de réhabilitation respiratoire à domicile. Enfin, cette idée de réhabilitation à domicile sans supervision ou supervisée à l'aide des nouvelles technologies de santé pourrait être compromise pour les patients atteints de dysfonctions cognitives. Ainsi, cette première partie cherche également à évaluer leur prévalence parmi les patients adressés en réhabilitation respiratoire.

La seconde partie de cette thèse cherche à évaluer la façon dont des outils existants ou de nouveaux outils pourraient être utilisés pour optimiser les effets du réentrainement à l'effort.

Enfin, la dernière partie de cette thèse propose de discuter des perspectives de recherche sur les thématiques abordées précédemment, ainsi que sur le maintien des bénéfices sur le long terme.

Première partie

I. Optimisation de l'accès à la réhabilitation respiratoire

Difficultés d'accès à la réhabilitation respiratoire : raisons et stratégies

Optimiser l'évaluation pour la rendre possible en ville ou à domicile

Nouvelles technologies pour favoriser la réhabilitation respiratoire à domicile

Fonction cognitive et réhabilitation respiratoire

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I.1. Difficultés d'accès à la réhabilitation respiratoire : raisons et stratégies

La réhabilitation respiratoire est recommandée par les sociétés savantes et organismes internationaux pour améliorer les symptômes et la qualité de vie des patients atteints de BPCO (8, 37, 38). Paradoxalement, et malgré le haut niveau de preuve supportant son efficacité (40), seuls 5% des patients qui pourraient bénéficier d'une telle approche thérapeutique y participent réellement (48-50). Cette problématique concerne également la France avec seulement 10% des patients bénéficiant de cette intervention (52). Cela s'explique par plusieurs facteurs dont un faible taux d'orientation vers les structures de réhabilitation (< 15%) (49, 53) ainsi qu'un fort taux de non-participation (jusqu'à 50% des patients adressés en réhabilitation ne s'y présentent jamais) (54). Plusieurs travaux se sont intéressés aux facteurs influençant l'orientation et la participation des patients aux programmes de réhabilitation (53-55). Parmi eux, le nombre limité de centres permettant l'évaluation initiale (dont l'épreuve d'effort cardiorespiratoire incrémentale) et la réhabilitation (principalement localisés dans les centres urbains) ainsi que les problèmes liés aux transports sont des facteurs majeurs (53-55). L'identification de ces barrières permet ainsi de mettre en place des stratégies alternatives visant à favoriser l'accès aux programmes de réhabilitation en facilitant l'évaluation initiale au plus près des patients tout en délocalisant la réhabilitation vers le secteur libéral ou au domicile des patients.

Cette problématique autour des difficultés d'accès à la réhabilitation respiratoire a récemment fait l'objet d'un éditorial que nous avons publié en 2020 dans *Journal of Physiotherapy*.

Editorial

Difficultés d'accès à la réhabilitation respiratoire dans la BPCO. Raisons et stratégies pour y faire face

Chronic obstructive pulmonary disease

T. Bonnevie and M. Elkins

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Editorial

Chronic obstructive pulmonary disease

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This editorial introduces *Journal of Physiotherapy*'s second article collection online. Each article collection is a collection of papers in a specific field of research, published in the *Journal of Physiotherapy* within the past decade and curated to facilitate access to important findings in that field, highlight trends in research in that field, and provide a scoping perspective on the implications for further research. They are collated on the journal's website (https://www.sciencedirect.com/journal/journal-of-physiotherapy/special-issues). The previous article collection addressed low back pain. The focus of this article collection is chronic obstructive pulmonary disease (COPD).

COPD is the fifth leading cause of death worldwide and its prevalence is increasing gradually.[1] The respiratory symptoms are progressive and lead to physical inactivity and muscle wasting, resulting in a spiral of worsening dyspnoea and deconditioning.[2] This all contributes to its very high global burden.

One of the key interventions to interrupt the progressive deconditioning is pulmonary rehabilitation. It has very worthwhile effects, including: reductions in dyspnoea and fatigue; improved emotional function and sense of control that individuals have over their condition; greater exercise capacity; and higher quality of life.[3] Despite these benefits, many patients who need pulmonary rehabilitation don't receive it because of issues such as poor referral rates, limited availability of pulmonary rehabilitation programs, difficulty accessing existing programs, and patient-related factors.[4,5] Of those referred to pulmonary rehabilitation, up to half will never even attend the program and as much as one-third will not complete the full course of rehabilitation.[6]

One of the most comprehensive reviews of the influences on pulmonary rehabilitation referral and participation is the paper by Cox et al[6] in this online article collection. Cox et al used the Theoretical Domains Framework to synthesise the results of 48 studies to demonstrate how pulmonary rehabilitation referral, uptake, attendance and completion were influenced by knowledge (eg, referral processes), beliefs (eg, expectations of outcomes), and environment (eg, travel, waiting time).[6] Their findings substantiate the recommendations in international guidelines to: improve awareness and knowledge of pulmonary rehabilitation among clinicians and patients; increase patient access to rehabilitation; and ensure the quality of rehabilitation programs.[6]

Although the review by Cox et al[6] does an excellent job of identifying the range of barriers to pulmonary rehabilitation, many of the included studies used convenience or purposive sampling; therefore, it is difficult to infer much about the relative prevalence of those barriers. One of the included studies that used representative sampling—and therefore provides robust data on the prevalence of various barriers to attendance and completion of pulmonary rehabilitation—is the study by Keating et al,[7] which is also in this online article collection. The most prevalent reason overall for non-attendance or non-completion was difficulty attending a centre-based program, due to difficulties with transport, mobility or cost.[7]

The findings of Cox et al and Keating et al presumably explain why so much research has investigated alternatives to the centre-based model, such as telerehabilitation.[8] Two systematic reviews evaluating telerehabilitation programs for people with cardiopulmonary disease concluded that telerehabilitation programs provide similar improvements in exercise capacity as centre-based programs[9] and have higher compliance rates.[10] Several of the papers in this online article collection have tackled the compex issues that are involved in delivering pulmonary rehabilitation outside the centre-based model.

One issue involved in telerehabilitation for people with COPD is the need for telecommunication and telemonitoring. Seidman et al[11] examined whether people attending metropolitan pulmonary rehabilitation reported that they were prepared to engage with telecommunication technology and whether they felt they had sufficient access and skills to use such devices. The responses from those patients indicated that physiotherapists who invest in establishing the infrastructure for pulmonary telerehabilitation can expect an ongoing and growing proportion of candidates who will be willing and able (either immediately or after some training) to use that format. The reported ability of pulmonary rehabilitation attendees to engage with technology adequately was later confirmed objectively in the study by Bonnevie et al.[12] In a study of over 100 adults with chronic respiratory disease who were referred to pulmonary rehabilitation, all could quickly learn to operate equipment used for remote monitoring of oximetry during home exercise. Almost all of the study participants also considered remote monitoring of oximetry acceptable. Furthermore, the oximetry data were transmitted with minimal artefact or invalid data.

Another issue is testing of exercise capacity for people undergoing home-based pulmonary rehabilitation. Where space is limited, physiotherapists may be tempted to complete a formal exerise test (such as the 6-minute walk test) on a shorter track than might be used in hospital-based rehabilitation. However, the study by Beekman et al.[13] warns that the results obtained with a shorter track are not equivalent—raising important caveats about the interpretation of the results and the use of predictive equations that were generated using data from tests conducted on a longer track.

Another issue involved in home-based rehabilitation is the exercise modality. Centre-based pulmonary rehabilitation typically uses exercise equipment, but use of such equipment for home-based pulmonary rehabilitation introduces expense, storage and transport requirements. Therefore, it is important to understand whether exercise-based rehabilitation can be as effective without the equipment. In an 8-week randomised trial, Leung et al examined whether a prescribed progressive walking training program conducted on flat

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ground could be as effective as training on a cycle ergometer.[14] They found that ground walk training increased endurance walking capacity more than cycle training, and was similar to cycle training in improving peak walking capacity, peak and endurance cycle capacity and quality of life. This study therefore provides evidence for ground walking as a mode of exercise training in pulmonary rehabilitation programs generally, as well as for home-based pulmonary rehabilitation. The greater improvement in endurance walking capacity presumably reflects specificity of training. Nevertheless, the result is particularly welcome because walking is a more typical activity of daily life than cycling for most people with COPD. This suggests that it might improve both symptoms during the many activities of daily living that involve walking, and self efficacy.

Because walking training program is achievable without specific equipment and can be performed in the home environment, it may also help the transition to long-term maintenance of exercise after formal pulmonary rehabilitation ends. The study by Hogg et al shows that people completing centre-based pulmonary rehabilitation report that they need ongoing, structured and socially supportive exercise opportunities in order to have the self-efficacy to maintain an active lifestyle.[15] Indeed, self-efficacy for physical activity and insight into its benefits are characteristics that physiotherapists might instil in people with COPD, as recommended in the study by Hartman et al.[16]

After pulmonary rehabilitation, sustaining the immediate benefits obtained from pulmonary rehabilitation may not be the only purpose of maintenance exercise. The analysis of long-term data by McKeough et al shows that maintaining physical activity and avoiding prolonged sedentary periods has a mortality benefit and lowers the odds of developing diabetes.[17] This finding generates an important implication for physiotherapists to not just encourage people with COPD to adhere to activity recommendations but also seek ways in which sedentary behaviour could be reduced.

Of course, physiotherapy management of COPD is not limited to pulmonary rehabilitation. Physiotherapists have much to offer during the acute exacerbations that punctuate the clinical course of COPD. Fortunately for readers of *Journal of Physiotherapy*, Professor Anne Holland's invited topical review expertly summarises the available evidence about physiotherapy management of acute exacerbations of COPD.[18] Other studies in this online article collection also address strategies to improve respiratory mechanics.[19,20]

In summary, this online article collection includes a range of important developments in research into physiotherapy management of COPD. The study designs address causation,[15] treatment,[13,18–20] assessment,[12–14] and barriers to traditional pulmonary rehabilitation,[6,7] remote pulmonary rehabilitation,[11,12] and subsequent physical activity.[15–17] Importantly, each paper has clear implications for clinical physiotherapists, which are identifiable in the paper's 'What this study adds' summary box.

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I.2. Objectifs de la première partie

L'objectif des contributions originales présentées dans cette première partie sont :

1. Évaluer la possibilité d'utiliser un test de terrain facilement réalisable au domicile des patients ou en cabinet libéral de kinésithérapie pour prescrire le réentrainement en endurance et le renforcement musculaire périphérique.
2. Évaluer la faisabilité, la validité et l'acceptabilité d'un outil de telemonitoring qui permet de proposer un programme de réhabilitation respiratoire à domicile avec un niveau de supervision équivalent à celui réalisé en centre.
3. Évaluer la prévalence de la dysfonction cognitive dans ce contexte d'une optimisation de la réhabilitation à domicile parmi les patients atteints de BPCO adressés en réhabilitation respiratoire et évaluer les effets à moyen terme de la réhabilitation respiratoire sur les fonctions cognitives

I.3. Optimisation de l'accès à la réhabilitation respiratoire : utilisation d'un test de terrain pour prescrire le réentrainement à l'exercice

L'évaluation initiale est une étape incontournable pour la mise en place d'un programme de réhabilitation respiratoire (8, 37, 38). Elle est très large afin de prendre en compte le caractère systémique de la BPCO. Il est recommandé d'inclure tous les éléments qui pourront être abordés durant le programme de réhabilitation respiratoire (Tableau 1).

Tableau 1 : *Bilan initial avant réhabilitation respiratoire. Issu des Recommandations pour la Pratique Clinique – Prise en charge de la BPCO, Rev Mal Respir 2010 (8).*

	Situation instable : post réanimation	Situation stable : bilan minimal	Situation stable : bilan optimal
Evaluation clinique Nutritionnelle psychologique	X	X	X
Tabagisme	X	X	X
Diagnostic éducatif	X	X	X
Test de marche en 6 minutes	X dès que possible	X	X
Gazométrie de repos	X	X	X
Force des muscles périphériques	X	X	X
Evaluation de la dyspnée	x	X	X
Qualité de vie	X	X	X
Spirométrie après BD	X	X	
EFR complète incluant la pléthysmographie			X
Epreuve d'exercice complète			X
ECG d'effort avec saturation et dyspnée	X dès que possible	X	
Force des muscles respiratoires			X

Ainsi, la Société de Pneumologie de Langue Française recommande comme évaluation optimale la réalisation d'une épreuve d'effort cardiorespiratoire complète ainsi que l'évaluation

de la force des muscles périphériques (notamment du quadriceps). Le but de l'épreuve d'effort cardiorespiratoire est double : 1) réaliser un électrocardiogramme d'effort afin d'identifier une ou plusieurs contre-indications cardiologiques au réentrainement à l'effort ainsi que 2) prescrire une intensité d'exercice adéquate pour l'entrainement en endurance (souvent au seuil ventilatoire) (8, 56). Cependant, cette évaluation nécessite du matériel spécialisé ainsi que du personnel formé, qui ne sont disponibles que dans peu de centres et dans lesquelles le délai d'attente est souvent long (57). Une stratégie alternative pourrait être le recours à une évaluation cardiaque isolée (nécessitant moins de matériel et étant plus accessible) couplée à un test de terrain (déjà réalisé dans le cadre de l'évaluation initiale) pour déterminer une intensité d'entrainement (58).

D'autre part, la mesure de la résistance maximale soulevée 1 fois (1RM ; correspondant au poids pouvant être levé, poussé ou tiré seulement une fois sans compensation) est le *Gold standard* pour évaluer la force musculaire périphérique (37, 59-61). Elle est également nécessaire pour prescrire le renforcement musculaire (souvent à 70% de la résistance maximale soulevée une fois (1RM) (37, 62-65)), seconde composante de l'entrainement à l'exercice proposé durant la réhabilitation respiratoire. Cependant, cette mesure nécessite également un personnel formé, une période d'apprentissage (nécessite du temps pour obtenir une mesure valide) et peut être potentiellement traumatique pour des patients avec des comorbidités telles que celles présentes dans la BPCO (60, 61). Ainsi, elle peut être difficile à obtenir en raison de la douleur ou de la fatigue musculaire alors même qu'un entrainement sous maximal, à 70% de la 1RM serait tout à fait possible. Dans la mesure où les tests de terrain, déjà réalisés dans le cadre de l'évaluation initiale avant réhabilitation respiratoire sont souvent liés à la force musculaire du quadriceps (66-68), ils pourraient être également utilisés pour estimer la 1RM et ainsi prescrire le renforcement musculaire périphérique.

Le test stepper de 6 minutes est un test de terrain récemment validé pour évaluer la capacité à l'exercice des patients atteints de BPCO (69-71). A l'inverse du test de marche de 6 minutes, largement utilisé mais dont la standardisation nécessite un couloir de 30 mètres afin d'obtenir une mesure reproductible (72, 73), le test stepper a l'avantage d'être facilement réalisable en pratique de ville (consultation médicale spécialisée ou kinésithérapeute libéral), ou même au domicile des patients. L'objectif des contributions originales présentées ci-dessous est d'évaluer son utilisation pour prescrire l'intensité d'entrainement à l'exercice (entrainement en endurance et renforcement musculaire).

Étude n°1

Utilisation du test stepper de 6 minutes pour prescrire l'intensité de l'entrainement en endurance pour des patients atteints de BPCO

Six-minute Stepper Test to Set Pulmonary Rehabilitation Intensity in Patients with COPD – A Retrospective Study

T. Bonnevie, FE. Gravier, M. Leboullenger, C. Médrinal, C. Viacroze, A. Cuvelier, JF. Muir, C. Tardif and D. Debeaumont

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Six-minute Stepper Test to Set Pulmonary Rehabilitation Intensity in Patients with COPD – A Retrospective Study

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ABSTRACT

Pulmonary rehabilitation (PR) improves outcomes in patients with chronic obstructive pulmonary disease (COPD). Optimal assessment includes cardiopulmonary exercise testing (CPET), but consultations are limited. Field tests could be used to individualize PR instead of CPET. The six-minute stepper test (6MST) is easy to set up and its sensitivity and reproducibility have previously been reported in patients with COPD. The aim of this study was to develop a prediction equation to set intensity in patients attending PR, based on the 6MST. The following relationships were analyzed: mean heart rate (HR) during the first (HR_{1-3}) and last (HR_{4-6}) 3 minutes of the 6MST and HR at the ventilatory threshold (HRvt) from CPET; step count at the end of the 6MST and workload at the Ventilatory threshold (VT) (Wvt); and forced expiratory volume in 1 second and step count during the 6MST. This retrospective study included patients with COPD referred for PR who underwent CPET, pulmonary function evaluations and the 6MST. Twenty-four patients were included. Prediction equations were $HRvt = 0.7887 \times HR_{1-3} + 20.83$ and $HRvt = 0.6180 \times HR_{4-6} + 30.77$. There was a strong correlation between HR_{1-3} and HR_{4-6} and HRvt ($r = 0.69$, $p < 0.001$ and $r = 0.57$, $p < 0.01$ respectively). A significant correlation was also found between step count and LogWvt ($r = 0.63$, $p < 0.01$). The prediction equation was $LogWvt = 0.001722 \times$ step count $+ 1.248$. The 6MST could be used to individualize aerobic training in patients with COPD. Further prospective studies are needed to confirm these results.

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KEYWORDS
Cardiopulmonary exercise testing; COPD; field test; pulmonary rehabilitation; six-minute stepper test

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of disability and mortality worldwide (1,2). The most significant symptoms are dyspnea and exercise limitation, leading to physical inactivity and muscle wasting (3). Most treatments address these symptoms and pulmonary rehabilitation (PR) has been shown to be effective in improving dyspnea, exercise capacity, and quality of life (4). Moreover, PR helps to reduce the number of exacerbations, length of hospital stay after an exacerbation, and mortality following an exacerbation (5).

Despite these benefits, only a small number of patients with COPD undergo PR (6). The main factor limiting access to these programs is a lack of PR centers. Thus, PR could be carried out of hospital or pulmonary centers. Another factor limiting access to these programs is a lack of assessment centers (7). Optimal assessment should include cardiopulmonary exercise testing (CPET) to determine both the optimal training settings as well as any cardiopulmonary contraindications to PR. However, this is not available in most centers and when it is, consultations are limited. Therefore, PR is often delayed for several weeks and patients can lose motivation.

In order to promote PR, CPET could be replaced by field tests to assess exercise capacity and individualize PR in patients with COPD. The 6-minute walk test (6MWT) is currently the gold standard to assess exercise capacity and can accurately predict a target heart rate (HR) for training in patients with COPD (8,9). However, the test has some disadvantages such as environmental constraint (requires a 30m-long corridor to be performed) which can limit it use in some centers and in ambulatory settings.

The 6-minute stepper test (6MST) is a new field tool. It consists of performing the largest number of steps on a stepper for 6 minutes. Its sensitivity and reproducibility have previously been reported in patients with COPD (10–13). It is easy to set up in the clinical setting and could be used to individualize PR in patients with COPD.

The aim of this study was to develop a prediction equation to set rehabilitation intensity for patients attending PR, with the use of a simple, readily available field test.

Methods

Study design and patient selection

This retrospective study included patients with COPD referred for PR from September 2015 to August 2016 to the ADIR Association, Bois-Guillaume, France.

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Inclusion criteria

Patients were included if they had a clinical diagnosis of COPD (ratio between forced expiratory volume in one second [FEV1] and forced vital capacity [FCV] <0.70). The severity of airflow limitation was assessed according to the GOLD classification (14). They had to be at least 18 years old and have undergone both CPET and pulmonary testing, and a 6MST during their first session of PR. They had to be below or equal to 90 kg (maximum weight supported by the stepper).

Non-inclusion criteria

Patients were not included if they had any heart rate modulating treatment (i.e. beta blockers, pacemakers), orthopedic disorders limiting the achievement of the 6MST, or had experienced a pulmonary exacerbation between the CPET and 6MST.

Exclusion criteria

Patients were excluded from the analysis if data from the 6MST were uninterpretable due to technical problems or if CPET had not determined the ventilatory threshold (i.e. CPET with oxygen or submaximal exercise), or suspected cardiac disorders on electrocardiogram during CPET.

Data extraction

Data regarding age, gender, height, weight, body mass index (BMI), pulmonary function, exercise capacity (CPET and 6MST), cardiovascular comorbidities, use of domiciliary noninvasive ventilation and long-term oxygen were extracted though a retrospective chart review.

Assessment

6MST

Patients performed two 6MSTs (Athlitec, GoSport, Sassenage, France) separated by a rest period of at least 20 minutes. The second test began when the HR and transcutaneous oxygen saturation (SpO_2), values returned to baseline values. Performance on the second test was often better because (1) the hydraulic jacks used in this study were more flexible once they had warmed-up and (2) there is a probable "learning" effect. (10–12) Standardization of the instructions for the 6MST was based on the ATS guidelines for the 6MWT (15), as previously described by Borel et al. (10):

"The object of this test is to make the highest number of strokes you can during six minutes duration. Six minutes is a long time, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but you have to resume exercise as soon as you are able. The correct movement is the one: you have to stretch the bent leg until the step has touched the stepper base. Then do the same movement with the other leg."

The test was performed in an isolated room in order to avoid noise or external stimuli which can affect performance. The stepper was placed near a door and the patient was allowed to put a hand on it if out of balance or exhausted. The height of the step was fixed to 20 cm. (10) A step was defined as the rise and lowering of one foot. The patient was informed of the time each minute. No other encouragement was given. HR and SpO_2 were continuously recorded by pulse oximetry (Oxymontre NONIN 3150, Nonin Medical Inc., Plymouth, MN) and then extracted by Nvision software (Henrotch, Aartselaar, Belgium).

CPET

CPET was performed on an electromagnetic ergometer (Ergoselect 200, Ergoline, Bitz, Germany) with an incremental protocol. Following a 3 minutes warm-up period, incremental ramp exercise (5–20 W/min) was maintained up to until exhaustion. A face mask (Hans Rudolph, Inc., Kansas city, MO, USA), pneumotach, and gaz analyzer (Ergocard, Medisoft, Louvain, Belgium) were used to measure gases (oxygen comsuption (VO_2) and carbon dioxide production (VCO_2)) breath by breath. Ventilatory threshold was manually determined as the average of 4 methods: (1) first break, (2) raise in the Minute ventilation (VE)/VO_2 ratio without modification of the VE/VCO_2 ratio (Wasserman's method), (3) raise in the raise in the expired carbonic gaz ($PetCO_2$) and (4) Beaver's method (16,17). HR was continuously monitored with a 12-lead electrocardiogram (Ergocard, Medisoft, Louvain Belgium).

Pulmonary function

Pulmonary function tests were carried out according American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines with plethysmography (Masterscreen, Jaeger, Wittsburg, Germany). Values were expressed as percentages of established theoretical values for European populations.

Outcome

Primary outcome was the development of the regression équations to predict the HR at the ventilatory threshold (HRvt) from the mean HR during the first (HR1-3) and last (HR4-6) 3 minutes of the 6MST. HR during these periods was averaged from the considered 3 minutes with a sampling frequency of 1 Hz and Nvision software.

Secondary outcomes were (1) the correlation between mean HR_{1-3} and HR_{4-6} from the 6MST, and the HRvt from CPET, (2) the relationship between step count at the end of the 6MST and the workload at the ventilatory threshold (Wvt), and (3) the relationship between forced expiratory volume in 1 second (FEV1) and the number of steps carried out during the 6MST.

Statistical analysis

Continuous data were expressed as means (SD) or medians (25th–75th percentile) as appropriate. Normality of the distributions was assessed using the Shapiro–Wilk test. The relationship between HR during the different tests as well as step count and Wvt were determined using Pearson or Spearman correlation tests according to the normality of the data distribution. Single linear regressions were performed when appropriate. Since the data for Wvt were not normally distributed, they were normalized using a log-transformation. A predictive equation using linear regression was then derived. Comparison between mean HR_{1-3} and HR_{4-6} was carried out using a paired *t*-test. Values from the second 6MST were used for the analysis. A *p*-value <0.05 was considered statistically significant. Prism 5 software was used for all analyses.

Table 1. Patient characteristics ($n = 24$).

Variable (units)	
Female (*n*)[a]	6 (25)
Age (years)[b]	61.5 (8.7)
Height (cm)[b]	167.2 (7.4)
Body mass (kg)[b]	65.9 (12.2)
BMI (kg/m²)[b]	23.6 (4.2)
FEV1 (L)[b]	1.23 (0.4)
FEV1 (%)[c]	45 (31.8–55)
FVC (L)[b]	2.73 (0.7)
FVC (%)[b]	79.8 (17.1)
FEV1/FVC (% ratio)[b]	45.4 (12.7)
COPD stage	
GOLD I[a]	1 (4)
GOLD II[a]	10 (42)
GOLD III[a]	9 (38)
GOLD IV[a]	4 (17)
6MST (steps)[b]	186.8 (59.4)
HR_{1-3}[b]	107.1 (14,3)
HR_{4-6}[b]	120.6 (15)
Power-vt (W)	37.5 (30–47.5)
Long-term oxygen (*n*)[a]	7 (29)
Non-invasive ventilation (*n*)[a]	2 (8)
Peripheral arterial disease (*n*)[a]	3 (13)
Hypertension	7 (29)
Hypercholesterolemia (*n*)[a]	3 (13)
Diabetes (*n*)[a]	1 (4)
Myocardial infarction (*n*)[a]	2 (8)

[a] Values expressed as numbers (%).
[b] Values expressed as means (SD).
[c] Values expressed as medians (25th–75th percentile).
FEV1/FVC is expressed as percentage ratio.
BMI: body mass index; FEV1: forced expiratory volume in one second; FCV: forced vital capacity; 6MST: 6-minute stepper test; HR_{1-3}: mean HR during the first 3 minutes of the 6MST; HR_{4-6}: mean HR during the last 3 minutes of the 6MST; Power-vt: Power at the ventilatory threshold.

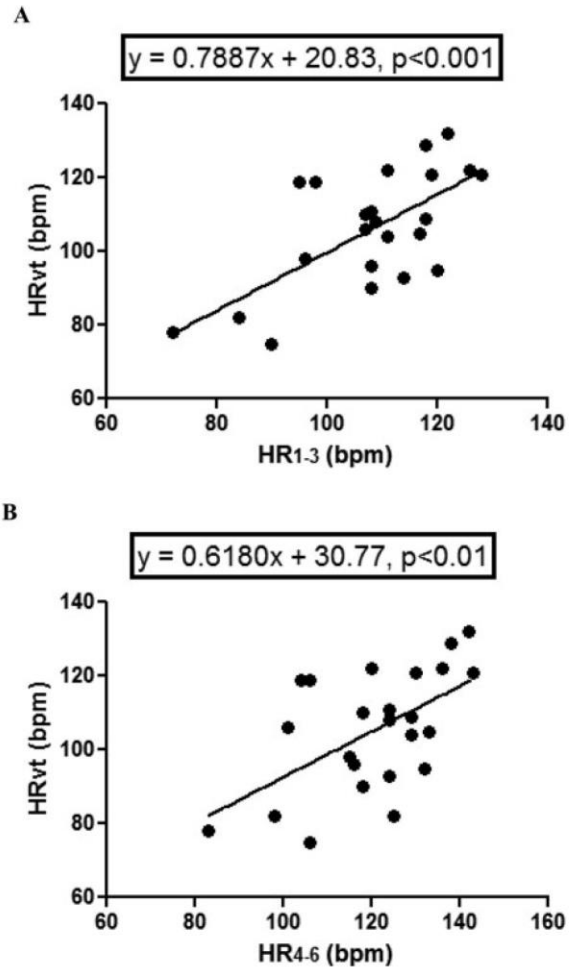

Figure 1. Relationship between mean HR during the first (A) and last (B) 3 minutes of the 6MST, and HR at the ventilatory threshold measured by CPET. HR: heart rate; HRvt: heart rate at the ventilatory threshold; HR_{1-3}: mean HR during the first 3 minutes of the 6MST; HR_{4-6}: mean HR during the last 3 minutes of the 6MST; CPET: cardiopulmonary exercise testing; 6MST: 6-minute stepper test.

Results

Patients

Among the 132 patients referred for PR during the study period (i.e. all types of respiratory diseases included), 37 met the inclusion criteria. 4 were excluded from the analysis due to technical problems during the recording of HR and SpO_2 during the 6MST. A further 9 patients were excluded from the analysis because the ventilatory threshold was not determined (i.e. patients exercising with oxygen or submaximal CPET). Thus data from 24 patients were analyzed.

Patient characteristics are presented in Table 1. Briefly, 25% were female, mean age was 61.5 (SD 8.7) years, mean BMI was 23.6 (SD 4.2) kg/m², median FEV1 was 45 (range 31.8–55) %, mean step count during the 6MST was 186.8 (SD 59.4) steps, and median power at ventilatory threshold was 37.5 (range 30–47.5) W. Seven patients (29.2%) used long-term oxygen and 2 patients (8.5%) used domiciliary non-invasive ventilation.

HR_{1-3} (101.1 (SD 14.3) bpm) was significantly lower than HR_{4-6} (114.3 (SD 15) bpm, $p < 0.0001$).

Regression equations for HR from 6MST and HR from CPET

HR from CPET could be predicted, respectively for HR_{1-3} (Figure 1A) and HR_{4-6} (Figure 1B) by the following equations:

- $HRvt = 0.7887 \times HR_{1-3} + 20.83$;
- $HRvt = 0.6180 \times HR_{4-6} + 30.77$.

Correlation between HR from 6MST and HR from CPET

There was a strong positive correlation between mean HR_{1-3} and HRvt from CPET ($r = 0.69$, $p < 0.001$).

There was also a strong positive correlation between mean HR_{4-6} and the HRvt from CPET ($r = 0.57$, $p < 0.01$).

Regression and correlation between step count and Wvt

There was a strong positive correlation between step count and Wvt ($r = 0.59$, $p < 0.01$). Since data were non-normally distributed, Wvt was normalized using a log-transformation to derive a predictive equation using linear regression. There was a strong positive correlation between the step count and LogWvt ($r = 0.63$, $p < 0.01$). LogWvt from the CPET could be predicted by the following equation:

- $LogWvt = 0.001722 \times \text{step count} + 1.248$.

Correlation between step count and FEV1

There was no significant relationship between step count and FEV1 expressed either as liters ($r = -0.1$, $p = 0.657$) or as a percentage of the theoretical norm ($r = -0.05$, $p = 0.8$).

Discussion

The results of this study showed that there were strong relationships between the means of both HR_{1-3} and HR_{4-6} from the 6MST and HRvt ($r = 0.65$ and $r = 0.53$ respectively). Thus, target heart rate for training in patients with COPD may be predicted by the following equations:

- $HRvt = 0.7887 \times HR_{1-3} + 20.83$;
- $HRvt = 0.6180 \times HR_{4-6} + 30.77$.

The mean HR from the last 3 minutes was chosen for analysis based on a previous report by Bonnet et al. (9). They used the mean HR from the last 3 minutes of the 6MWT (also called "straight HR") to predict HRvt with the following equation:

- $HRvt = (0.75 \times HRstraight) — (0.03 \times distance) — (0.32 \times age) + 64.4$.

Moreover, Borel et al. (10) showed that there was no difference between the mean HR of the last 3 minutes of each test (respectively 118.2 (SD 18.7) bpm for the 6MST and 120.8 (SD 12.6) bpm for the 6MWT). However, HR kinetics may differ between tests. Pichon et al. reported a significantly higher HR at the end of the 6MST than at the end of the 6MWT (13). This was also suggested in patients with interstitial lung disease (18). Based on these findings and on our personal experience, we also chose to evaluate the first 3 minutes of the 6MST. As expected, the correlation between HR_{1-3} and HRvt was stronger than between HR_{4-6} and HRvt. This could be attributed to the significant difference between HR_{1-3} and HR_{4-6} (i.e lower HR during the first part of the test). These results are in accordance with findings in patients with interstitial lung disease during the 6MST, showing a gradual increase in HR throughout the test, while in the 6MWT, HR stabilized around the 3rd minute. HR was also significantly higher during the 6MST than during the 6MWT (18). This might suggest that the first part of the 6MST, during which HR was lower, may reflect aerobic exercise whereas the last part of the 6MST may reflect an exertion that gradually reached maximal oxygen consumption, as suggested in patients with interstitial lung disease during a 6-minute step test (19). Nevertheless, this assumption should be specifically assessed in future studies. The stronger correlation of mean HR_{1-3} with HRvt and lower HR suggests that mean HR_{1-3} should be used to individualize exercise intensity in patients with COPD.

To our knowledge, this is the first study to compare HR during the 6MST and HRvt. This is important clinically because it has direct implications for the determination of the level of aerobic training for each individual. Moreover, CPET is considered as the optimal assessment for patients with COPD prior to PR. However, it is probably not necessary for every patient, particularly for those in the earlier stages of the disease. Thus, a medical and cardiac exercise evaluation, in association with a field exercise capacity test could be sufficient to determine an appropriate PR program for some patients with COPD.

These results are in agreement with those reported by Grobois et al. (12). They also found a relationship between Wvt and the step count during 6MST. The workload intensity for training in patients with COPD could be predicted by the following equation: $LogWvt = 0.001722 \times step\ count + 1.248$. For example, a patient who performed 190 steps (approximately the mean observed in this study) could initially be trained at 35–40 W. However, it is important to remember that whether the prescription of intensity is based on CPET or derived from a field test, it simply provides an indication of the appropriate intensity at which to start training, and should then be adapted to patient's tolerance (dyspnea or muscle fatigue) (20, 21). Unfortunately, we could not compare this equation with the data from Grobois et al. because they did not perform linear regression and did not discuss this outcome. Nevertheless, it has important clinical implications and further studies, should be performed to validate the use of this equation for the implementation of optimal PR.

This study compared effort on a stepper and on an ergometer. Since the effort provided on each is substantially different, some parameters could have influenced the results, including muscle mass, weight, and balance. As weight and balance were both controlled by the inclusion criteria (weight <90 kg and ability to perform the 6MST), it is unlikely that they strongly influenced the results. The type of exercise also influences cardiopulmonary parameters. For example, Pichon et al. found a significantly higher level of desaturation during the 6MWT than during the 6MST. They attributed this to differences in the biomechanical and metabolic requirements of the tests (13). It could be hypothesized that similar differences exist between the effort carried out on a stepper and on an ergometer. Moreover, variations in individual dynamic hyperinflation and lung mechanics may also occur in response to a specific exercise.

Finally, the results showed no significant relationship between step count and respiratory function (FEV1). This is not surprising because there is only a weak-to-moderate positive association between FEV1 and objectively measured physical activity in patients with COPD (22).

The utility of equations for exercise prescription has recently been discussed by Kirkham et al. (23). They assessed the errors associated with exercise prescription based on estimated values from 11 equations (derived from the distance walked during the 6MWT) identified through their research. They concluded that the use of these equations for exercise prescription would result in a significant error (from 12 to 47%, depending on the method used) and should not be used to prescribe exercise intensity. A key point highlighted by the authors is that some of these equations were derived from data collected in the research setting, which may differ from data collected in clinical setting and thus limit their use for clinical purpose. As the present study was a retrospective clinical study, all assessments and data collections were carried out in the clinical setting. This likely strengthens the clinical relevance of our results. Nevertheless, the reliability of the equations found in this study need be tested in a new sample of patients. Furthermore, Kirkham et al. (23) discussed the utility of other methods of exercise intensity prescription, rather than the distance during the 6MWT, including the use of heart rate, which was used by Bonnet et al. (9) and in the present study.

This study has several limitations. First, we cannot rule out some bias due to it retrospective design. However, all assessments were standardized according to current guidelines and

data were collected in the clinical setting, strengthening the potential relevance of the determined equations (see above). Secondly, the device used to monitor HR may have been influenced by movement artifacts and electrocardiogram telemetry might have been more accurate. Equally, the accuracy and reliability of the device to measure heart rate during the 6MST has never been assessed and compared with telemetry. However, the specification and technical information (from the manufacturer) for the Nonin 3150 states an accuracy of more or a less 3 bpm with or without motion, and in the range of 40–240 bpm in conditions of low perfusion. This study was based in the clinical setting in which telemetry is not available but pulse oxymetry is commonly used. Pulse oxymetry is frequently used in research to monitor HR during field tests, particularly during the 6MST (10–12). Moreover, patients were in different stages of the disease, the sample was small and addressed a specific population undergoing PR. For example, patients were excluded if they weighed more than 90 kg, which is the weight limit supported by the device. Furthermore, they were mostly male, non-oxygen users, and were able to achieve the ventilatory threshold during CPET which might not reflect the whole population referred for PR. However, CPET is mostly necessary in the case of severe COPD and, ideally, should not be replaced by field tests in that population. Finally, the VT was selected by human observers. This has recently been questioned in patients with COPD and could have introduced some inter-individual error in HR at the VT in more severe patients (24). Thus, further studies should prospectively investigate the relationship between the 6MST and CPET in patients in the early stages of COPD (i.e. patients who can achieve the ventilatory threshold) in order to individualize their aerobic training.

Conclusion

The 6MST could be used to individualize aerobic training in patients with COPD in an ambulatory setting. Further prospective studies are needed to confirm these results and could focus on patients in the early stages of COPD.

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Declaration of interest

The authors state that they have no conflicts of interest.

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Étude n°2

Utilisation du test stepper de 6 minutes pour prescrire l'intensité de l'entrainement en endurance pour des patients atteints de BPCO légère à modérée – Une étude multicentrique observationnelle

Can the six-minute stepper test be used in clinical practice to determine the intensity for endurance training in people with early stage COPD: A multicenter observational study

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Can the six-minute stepper test be used to determine the intensity of endurance training in early stage COPD: A multicenter observational study

--Manuscript Draft--

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Article Type:	Original Research
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Abstract:	Background Cardiopulmonary exercise testing (CPET) is used to prescribe endurance training but is of limited access. Therefore, the priority for the available places is not given to those people with early stage COPD while they would benefit from PR. Research question Can the six-minute stepper test (6MST) be used to prescribe endurance training in early stage COPD patients. Study design and methods 50 patients with COPD (mean FEV 1 71% (SD16)) participated in this multicenter observational study and performed both a CPET and a 6MST to derive predictive equations of their heart rate at the ventilatory threshold (HRvt) during the CPET as well as the corresponding workload (Wvt). The equations were subsequently tested within this group as well as in an independent cross-validation group (31 patients). Results The 6MST successfully predicted HRvt (r 2=0.38,p<0.01) and Wvt (r 2=0.48,p<0.01). The MAD was 9bpm [95% CI: 7 to 10] for HRvt and 11W [95% CI: 8 to 13] for Wvt. The predicted HRvt was lower than the maximal HR achieved during the CPET for 98% of the subjects [95% CI: 89 to 100]. The external validity of these equations within the cross-validation group was not confirmed. Interpretation The 6MST is valid to start endurance training safely in people with early stage COPD.

	Some errors may occur at the individual level suggesting that the prescription may necessitate to be adjusted within the first exercise session. Because the external validity of these equations was not confirmed, they should not be used in other populations.
Suggested Reviewers:	
Opposed Reviewers:	

Dear Mark,

We are pleased to submit our manuscript "Can the six-minute stepper test be used to determine the intensity of endurance training in early stage COPD: A multicenter observational study" for consideration for publication in the *Journal of Physiotherapy.*

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The manuscript reports a study in the area of pulmonary rehabilitation (PR). While a large body of evidence support the effectiveness of PR for people COPD, as low as 5% of those people who would benefit from PR actually engage in. This is mainly due to the limited availability of both PR and evaluation centers and there is a need to develop strategies to increase participation. An effective alternative would be home-based PR but, even this model considers center-based exercise testing since cardiopulmonary exercise testing (CPET), the gold standard evaluation used to determine both the optimal training settings as well as any cardiopulmonary contraindications to PR cannot be performed out of centers. An alternative strategy would associate a cardiac exercise evaluation outside the center (less technical and more accessible than CPET to rule out any cardiac

contraindication) and an in-home field test to assess baseline exercise capacity and, at the same time, determine an appropriate intensity at which to start endurance training.

Therefore, the research question addressed by this multicenter observational study was to assess whether the six-minute stepper test (6MST) could be used to determine the intensity of endurance training in early stage COPD patients. To proceed, 50 patients with early stage COPD participated in both a CPET and a 6MST to derive predictive equations of their heart rate at the ventilatory threshold (HRvt) during the CPET as well as the corresponding workload (Wvt). The equations were subsequently tested comparing the estimated and the actually measured HRvt and Wvt within this group as well as in an independent cross-validation group of 31 patients.

The study answers an important clinical question since it showed that a field test, easy to perform in the home environment, is valid to estimate where to start endurance training safely in people with early-stage COPD.

We think this research is in keeping with the previously published studies on the thematic of home-based PR in COPD patients in the *Journal* and we have thought useful to support previous results by our original data.

The present manuscript is not submitted elsewhere. Possible reviewers are listed below. If you have any questions or if anything seems incomplete or not in order, please do not hesitate to contact myself.

Thank you for your consideration of our manuscript.
Yours sincerely,
Tristan Bonnevie

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Title: Can the six-minute stepper test be used to determine the intensity of endurance training in early stage COPD: A multicenter observational study

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3. has provided final approval of the version to be published;
4. has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Structured abstract

Background: Cardiopulmonary exercise testing (CPET) is used to prescribe endurance training but is of limited access. Therefore, the priority for the available places is not given to those people with early stage COPD while they would benefit from PR.

Research question: Can the six-minute stepper test (6MST) be used to determine the intensity of endurance training in early stage COPD patients.

Study design and methods: 50 patients with COPD (mean FEV1 71% (SD 16) participated in this multicenter observational study and performed both a CPET and a 6MST to derive predictive equations of their heart rate at the ventilatory threshold (HRvt) during the CPET as well as the corresponding workload (Wvt). The equations were subsequently tested within this group as well as in an independent cross-validation group (31 patients).

Results: The 6MST successfully predicted HRvt ($r^2=0.38$, $p<0.01$) and Wvt ($r^2=0.48$, $p<0.01$). The MAD was 9bpm [95% CI: 7 to 10] for HRvt and 11W [95% CI: 8 to 13] for Wvt. The predicted HRvt was lower than the maximal HR achieved during the CPET for 98% of the subjects [95% CI: 89 to 100]. The external validity of these equations within the cross-validation group was not confirmed.

Interpretation: The 6MST is valid to start endurance training safely in people with early stage COPD. Some errors may occur at the individual level suggesting that the prescription may necessitate to be adjusted within the first exercise session. Because the external validity of these equations was not confirmed, they should not be used in other populations.

Clinical Trial Registration: NCT02842463.

Key-words: COPD; six-minute stepper test; cardiopulmonary exercise testing; exercise; pulmonary rehabilitation.

Condensed abstract

50 patients with early stage COPD participated in this multicenter observational study and performed both a CPET and a 6MST to derive predictive equations of their heart rate at the ventilatory threshold (HRvt) during the CPET as well as the corresponding workload (Wvt). The 6MST successfully predicted HRvt and Wvt and the error that would occur when using these predictive equations lied within a pre specified margin of equivalence. The validity of the equations was not confirmed in an independent cross-validation group of 31 patients and suggest that they should not be used in other populations.

Abbreviations

BMI: body mass index.

COPD: chronic obstructive pulmonary disease.

CPET: cardiopulmonary exercise testing.

FEV1: forced expiratory volume in 1 second.

HR: heart rate.

HRvt: heart rate at the ventilatory threshold.

HR_{1-3}: mean heart rate during the first 3 minutes of the six-minute stepper test.

HR_{4-6}: mean heart rate during the last 3 minutes of the six-minute stepper test.

PR: pulmonary rehabilitation.

SpO2: transcutaneous oxygen saturation.

Wvt: workload at the ventilatory threshold.

6MST: six-minute stepper test.

Introduction

Pulmonary rehabilitation (PR) is widely recommended [2-4] in chronic obstructive pulmonary disease (COPD) since it effectively improves dyspnea, fatigue, emotional control, exercise capacity and quality of life [5]. Unfortunately, the main issue associated with PR is a very low utilization rate (as low as 5% of those people who would benefit from PR actually engage in) [6-8], mainly due to the limited availability of both PR and evaluation centers [6,9,10]. In this context, the priority for the available places is not given to those people with early stage COPD [8,11] (commonly the less symptomatic) while they would benefit from PR [11-13]. In addition, people with early-stage COPD are more likely to be socially active [14] which can limit their attendance to conventional center-based PR due to inconvenient timing [9,15,16]. An effective alternative for these people would be home-based PR [17]. However, even this model considers center-based exercise testing [18] since cardiopulmonary exercise testing (CPET), used to determine both the optimal training settings as well as any cardiopulmonary contraindications to PR cannot be performed out of centers due to a limited access as well as technical and safety issues.

An alternative strategy would associate a cardiac exercise evaluation outside the center (less technical and more accessible than CPET to rule out any cardiac contraindication) and an in-home field test to assess baseline exercise capacity and, at the same time, determine an appropriate intensity at which to start endurance training. While the 6-minute walk test is actually the gold standard to assess exercise capacity and prescribe a training intensity for people with COPD [19,20], any change of its established procedures to cope with the home environment constraints would result in clinically relevant errors [21]. Alternatively, the six-minute stepper test is a valid tool to assess exercise capacity in people with COPD and does not necessitate any adaptation to be performed at home [1,22,23]. Beyond informing about exercise capacity, recent data from our laboratory suggest that it may also be useful to

determine the intensity of endurance training [24,25] so that PR could be completely delivered at home. However, due to methodological limitations, further evidence is necessary before it can be used in clinical practice.

Therefore, the research questions addressed by this study are:

1. Can the 6MST be used to predict endurance training modalities (targeted heart rate and corresponding workload) in early stage COPD patients;
2. Are these predictions valid within the studied population;
3. Are these predictions valid within an independent cross-validation group.

Patients and method

Study design and participants: This prospective multicenter observational study was approved by the French Ethics Committee Nord-Ouest 1 (CPP-SC 011/2015) and was prospectively registered at www.clinicaltrials.gov (NCT02842463). The validity of the 6MST to prescribe endurance training intensity was assessed using a two steps procedure. First, people with COPD who were referred for PR at ADIR Association, Rouen University Hospital, France and Jacques Monod Hospital, Le Havre, France, were screened for eligibility between October 2016 and December 2019 and constituted the equation group. All these participants performed both a CPET and a 6MST during the evaluation process to initiate their PR. The 6MST was used to develop predictive equations of their heart rate (HR) at the ventilatory threshold (HRvt) during the CPET as well as the corresponding workload (Wvt), which are effectively used to set up an individualized exercise training [26]. The second step was to evaluate the error that would occur when using these predictive equations to prescribe exercise intensity compared to that from the CPET. For this purpose, the equations were tested within the equation group as well as in an independent cross-validation group using

individual participant data from a validation study of the 6MST [1]. Written consent was obtained from all participants.

Inclusion criteria

People were included if they had a clinical diagnosis of COPD and a ratio between the forced expiratory volume in one second (FEV1) and the forced vital capacity <0.70. They had to be 18 years and over, have a FEV1 ≥ 50% and a weight of 90kg or below (maximum weight supported by the stepper). People from [1] who had a FEV1 ≥ 50% and a ventilatory threshold derived from a CPET were included in the cross-validation group.

Non-inclusion criteria

People who had any heart rate modulating treatment (i. e. beta blockers, pace makers etc., excluding oral beta-2 agonist), had orthopedic or peripheral vascular disorders limiting the achievement of the 6MST, had suspected cardiac disorders on electrocardiogram during the CPET or experienced an acute exacerbation of COPD between the CPET and the 6MST were not included. Other non-inclusion criteria included a time frame superior to 3 months between the CPET and the possibility to perform the 6MST, pregnancy or likely to be and guardianship.

Assessment

Cardiopulmonary exercise testing: Detail of the procedure is shown in Appendix 1. The ventilatory threshold was manually derived as the average of 4 methods: first break in the minute ventilation curve, raise in the minute ventilation to oxygen consumption ratio without modification of the minute ventilation to carbon dioxide production ratio, raise in the end-tidal expired carbon dioxide gas and the Beaver's method [27,28]).

Six-minute stepper test: Participants performed two 6MSTs (Athlitec, Sassenage, France) as previously described [1,22,23,25]. Further details are available in the Appendix 1.

Pulmonary function: Pulmonary function testing was performed according to the European Respiratory Society guideline and expressed as percentages of established theoretical values for European populations [29].

Statistical analysis

Sample size calculation is shown in Appendix 2. The normality of the distribution was assessed using the Kolmogorov–Smirnov test and the D'Agostino & Pearson omnibus normality test. Categorical data were expressed as counts (%) and continuous data were expressed as mean (SD) or median (25th–75th percentile) according to the distribution. Baseline characteristics of both groups were compared with Fisher's test (for proportion) and independent Student's t-test or Mann–Whitney test (for continuous data), depending on the distribution. Specific analysis for the determination of the predictive equations as well as their validation are shown in Appendix 2. A p-value <0.05 was considered statistically significant in all cases. GraphPad Prism 5.03 and R 3.6.1 softwares were used for analyses.

Results

Patients: After 437 subjects were screened for eligibility, 50 were enrolled in the equation group (Figure 1). Their demographic characteristics are shown in Table 1. Briefly, 38% were female, their mean age was 61 years (SD 10) and their mean FEV1 was 71 % (SD 16) which was not significantly different from those people of the cross-validation group (Table 1). However, the cross-validation group had a significantly higher BMI than in the equation

group (28.6 kg/m² (SD 6.1) and 25.4 kg/m² (SD 5) respectively, p=0.01) and a lower forced vital capacity (%) (respectively 77 % (SD 19) and 101 % (SD 18), p<0.01).

Relationship between HRvt, Wvt and covariates (equation group): Supplementary Table 1. Since HR_{1-3} and HR_{4-6} were highly interrelated (r= 0,84, p<0.01) only HR_{1-3} was subsequently entered in the multivariate analysis.

Predictive equations (equation group):

HRvt: In the multivariate analysis, only HR_{1-3} and age remained significant independent predictors of HRvt (Table 2) and were conserved in the stepwise regression. HRvt can be predicted using the following equation (r^2= 0.38, p<0.01):

- HRvt *(bpm)* = (HR_{1-3} *(bpm)* x 0.6076) – (age *(yr)* x 0.3427) + 68.4967

Wvt: Step count during the 6MST was the only significant independent predictor of Wvt (Table 2) and was conserved in the stepwise regression. Wvt can be predicted using the following equation (r^2= 0.48, p<0.01):

- Wvt = (6MST *(steps)* x 0.17495) + 8.72148

Validation of the predictive equations:

Internal validity (equation group): Within the equation group, mean predicted and actually measured HRvt were not significantly different (114 bpm (SD 8) and 114 bpm (SD 13) respectively, p=0.99). The MAD was 9 bpm [95% CI: 7 to 10] and the mean bias was 0bpm (upper and lower bound ranging from -21 to 21 bpm) (Figure 2A). The predicted HRvt was lower than the maximal HR achieved during the CPET for 98% of the subjects [95% CI: 89 to 100].

There was also no significant difference between the mean predicted and actually measured Wvt (50 W (SD 13) and 51 W (SD 18) respectively, p=0.99). The MAD was 11 W [95% CI: 8 to 13] and the mean bias was 0 W (upper and lower bound ranging from -26 to 26 W) (Figure 2B).

At the individual level, 43 out of the 50 subjects (86% [95% CI: 74 to 94]) had a bias within the prespecified margin of equivalence for at least Wvt or HRvt among whom 22 had both (44% [95% CI: 31 to 58]). Additionally, 33 subjects (66% [95% CI: 52 to 78]) had a predicted Wvt within the margin of equivalence, and 100% of them [95% CI: 88 to 100]) had a bias for HRvt within the upper and lower bounds of the Bland-Altman analysis. The remaining 10 subjects had a predicted HRvt but not a predicted Wvt lying within the margin of equivalence.

External validity (cross-validation group): Within the cross-validation group, mean predicted and actually measured HRvt were not significantly different (113 bpm (SD 13) and 107 bpm (SD 21) respectively, p=0.21). The MAD was 13 bpm [95% CI: 9 to 18] and the mean bias was 6 bpm (upper and lower bound ranging from -25 to 38bpm) (Figure S1A). The predicted HRvt was lower than the maximal HR achieved during the CPET for 87% of the subjects [95% CI: 67 to 96].

Finally, there was no significant difference between the mean predicted and actually measured Wvt (53 bpm (SD 12) and 55 bpm (SD 24), p=0.69). The MAD was 18 W [95% CI: 12 to 23] and the mean bias was -2 W (upper and lower bound ranging from -49 to 45 W) (Figure S1B).

At the individual level, 16 out of 23 subjects whom were used to validate both equations (70% [95% CI: 49 to 85]) had a bias within the prespecified margin of equivalence for at least Wvt or HRvt among whom 8 had both (35% [95% CI: 19 to 55]).

Discussion

The results of this study show that the mean HR during the first 3 minutes of the 6MST and age were independent predictors of the HR used to prescribe endurance training during a CPET in people with early stage COPD. The corresponding workload was independently predicted only by the steps performed during the 6MST. Their use to estimate HRvt and Wvt to prescribe endurance training was overall valid within the equation group. However, clinically relevant errors may occur at the individual level (Bland-Atlman analysis). The cross-validation group did not confirm the validity of these predicted prescriptions since they were out of the range of the pre specified margin of clinical equivalence.

Relationship with HRvt and Wvt: Previous studies have shown moderate to large relationship between HRvt and HR at 60% of the HR reserve during the 6MST, HR_{1-3} and HR_{4-6} ($r= 0.48$, $r= 0.69$ and $r= 0.57$ respectively) in people with a wide range of COPD severity [25,30]. These results are extended by the present study which also found a significant relationship between HRvt and both HR_{1-3} and HR_{4-6} in people with early stage COPD [25]. With a more robust methodology, this confirms that the first 3 minutes of the 6MST are more related to HRvt than the last 3 but to a lesser extent than previously reported [25]. The addition of age to HR_{1-3} contributed to explain about 40% of the variance of HRvt.

The present results also show that Wvt was significantly related with the number of steps performed during the 6MST as previously suggested [25] and may explain up to an half of the variance of Wvt. Unsurprisingly, gender and FEV1 were also related with Wvt. However, they did not remain significant independent predictors in the multivariate analysis. Though the predictive model does not explain the remaining 50% of the variance, other clinical variables,

such as muscle strength may have contributed to improve it [31]. In addition, since stepping and cycling are substantially different, this have probably introduced some unexplained variability between the tests. However, the direct comparison of the cardiorespiratory and metabolic stress during both procedures has not been explored yet and should be further studied.

Definition of the margin of equivalence: The main issue when comparing two tests to prescribe exercise training is to assume how the measured difference may affect the benefit of PR and safety. Because exercise prescription based on HR is not a fixed value but rather a range of HR, we assumed that a 95% CI of the MAD lying within +/- 10bpm would lead to similar benefit. With regards to Wvt and considering from a practical point of view that expensive cycloergometer allowing for a 5W increments are not necessary to train people with early stage COPD (i.e. a 10 W increment is sufficient) we assumed that a 95% CI of the MAD lying within +/- 14 W would be clinically equivalent because it would be rounded to the nearest 10 W. Further data are necessary to confirm these assumed margins of equivalence which would be helpful to confirm the clinical validity of field test to prescribe exercise training.

Internal validity of the predictive model: Since the mean predicted HRvt and Wvt were not significantly different from the actually measured HRvt and Wvt respectively and that the 95% CI of the MAD (from 7 to 10 bpm) lied within the prespecified range of clinical equivalence, the predictive model can be considered valid at the group level. Even though the upper and lower bounds of the Bland-Altman analysis were narrower than previously suggested [24], they were out the range the margin of equivalence suggesting that the model may not suit perfectly at the individual level. Reassuringly, even this relative inaccuracy would not lead to exceed the maximal HR achieved the CPET so that the exercise prescription

is safe (only exceeded of 1 bpm for 1 subject). From a pragmatic clinical point of view, even though the initial intensity of PR is based on a comprehensive CPET (using either HRvt or Wvt) or any other modality, it simply provides an indication of the intensity at which to start safely and may necessitate to be subsequently adapted within the first training session. Based on the present results, it is possible to determine an intensity where to start endurance training for more than 85% of the subjects. We would recommend for clinical practice to use the equation for Wvt and check that the corresponding HR lies within 20 bpm of the estimated HRvt (would suit for two thirds of the subjects). Any discrepancy could easily be resolved by adjusting the workload based on the estimated HRvt for the remaining subjects (Figure 3).

External validity of the predictive model: Although the estimated and actually measured HRvt and Wvt were not significantly different, the 95% CI of the MAD for HRvt [9 to 18 bpm] and Wvt [12 to 23 W] were out of the margin of equivalence. This was further evident at the individual level and we did not find any association between the predicted Wvt and HRvt for them to be used in an acceptable way in clinical practice for a sufficient proportion of patients. Because the cross-validation group was not restricted to those people with a weight inferior to 90 kg to better reflect daily life practice, demographic characteristics of both groups were not similar. Particularly, the difference in BMI may be of worth importance while stepping and probably contribute to explain the discrepancies between estimated and actually measured prescriptions. Another explanation may also lie in the method used to assess HR. While it was continuously monitored in the equation group and averaged over the first 3 minutes of the 6MST using all the available data, it was punctually assessed every minute in the cross-validation group. Although this reflects daily clinical practice, this may not be accurate enough to prescribe exercise training since any artefact in any of the three measurements may lead to substantial error. Therefore, we suggest that the use of the

equations should remain limited to those people with a weigh inferior to 90 kg who were assessed using a continuous monitoring of HR.

Limits of the study: The main limit of this study is that we did not reach the pre specified sample size and prematurely stopped the recruitment since we only included 50 participants in two centers over a 3 years period. This reflect the already known difficulty to recruit people with early stage COPD for center-based PR and further justifies the use of field test to quickly assess these subjects and deliver in-home PR. Despite this, we were still able to derive a predictive equation with good internal validities. In addition, this moderate sample size may also explain the wide upper and lower bounds observed in the Bland-Altman analysis. The second limit of this study is that we failed to show the validity of the predictive equations in an independent cross-validation group [1]. Therefore, their utilization should be limited to those people with similar characteristics than those included in the present study.

This study suggests that the use of the 6MST is valid at the group level to estimate where to start endurance training safely in people with early-stage COPD. However, some errors may occur at the individual level which suggest that the prescription may necessitate to be adjusted for some people within the first exercise. Because the external validity of these equations was not confirmed, they should not be used in other populations, such as those heavier than 90 kg. Further studies should now assess the validity of these equations in a cross-validation group with similar demographic characteristics and using a continuous HR monitoring as well as to compare face to face the effects of a PR program whose intensity has been prescribed directly from a CPET or derived from the 6MST using a randomized comparative design.

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Legends of the figures

Figure 1: Flow chart.

Figure 2: Bland-Altman plots for the prescription of HRvt within the equation group (A) and the prescription of Wvt within the equation group (B) using the predictive equations derived from the six-minute stepper test. The point-to-point difference between the two prescriptions (estimated minus actually measured) is plotted against the mean of the two prescriptions.

Figure 3: Algorithm to set training intensity according to the six-minute stepper test for people with early stage COPD.

Table 1. Demographic characteristics of the patients.

Characteristics	Patients		Between-group comparison
	Prediction group (n = 50)	Cross-validation group (n = 31)	*p*
Gender, n female (%)	19 (38)	6 (19)	0.08
Age *(yr)*, mean (SD)	61 (10)	59 (9)	0.26
Height *(cm)*, mean (SD)	166 (9)		
Body mass *(kg)*, median (IQR)	70 (57 to 84)		
Body mass index *(kg/m²)*, mean (SD)	25.4 (5)	28.6 (6.1)	**0.01**
FEV_1 *(L)*, mean (SD)	1.9 (0.6)	2.1 (0.4)	0.28
FEV_1 *(%)*, mean (SD)	71 (16)	67 (12)	0.16
FVC *(L)*, mean (SD)	3.4 (0.9)	3.4 (0.7)	0.81
FVC *(%)*, mean (SD)	101 (18)	77 (19)	**< 0.01**
FEV_1/FVC *(%)*, median (IQR)	57 (49 to 65)	62 (54 to 67)	**< 0.01**
Residual volume to total lung capacity, mean (SD)	0.5 (0.1)		
VO_{2peak} *(ml/kg/min)*, mean (SD)	16 (5)	15 (5)	0.61
W_{peak} *(W)*, mean (SD)	87 (30)	95 (29)	0.21
6MST *(steps)*, mean (SD)	239 (73)	255 (72)	0.32
Comorbidities			
Hypertension, n (%)	9 (18)		
Hypercholesterolemia, n (%)	9 (18)		
Diabetes, n (%)	6 (12)		
Cardiopathies, n (%)	5 (10)		
Lung cancer, n (%)	16 (32)		
Other cancer, n (%)	9 (18)		

Fisher test for categorial data. Mann-Whitney or independent t-test for other characteristics.

Percentages may not sum to 100 due to rounding.

FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, VO_{2peak} = maximal oxygen consumption, W_{peak} = maximal workload achieved during cardiopulmonary exercise testing, 6MST = six-minute stepper test.

Table 2. Multivariate analysis of predictors of HRvt and Wvt.

Independent predictors	Dependent variable			
	HRvt (n = 50)		Wvt (n = 50)	
	Estimate	*p*	*Estimate*	*p*
HR_{1-3} *(bpm)*	**0.5824**	**<0.01**		
Age *(yr)*	**-0.3362**	**0.05**		
Fatigue *(Borg)*	-0.6309	0.42	-0.70022	0.47
Gender			6.56292	0.14
FEV1 *(L)*, mean (SD)			-0.07123	0.99
6MST *(steps)*			**0.15900**	**<0.01**
Intercept	**74.1470**	**p<0.01**	12.26060	0.247

Multivariate analysis.
HRvt: $r^2 = 0.38$, $p<0.01$.
Wvt: $r^2 = 0.52$, $p<0.01$.

HRvt = heart rate at the ventilatory threshold, Wvt = workload at the ventilatory threshold, HR_{1-3} = mean heart during the first 3 minutes of the six-minute stepper test, HR_{4-6} = mean heart rate during the last 3 minutes of the six-minute stepper test, FEV1 = forced expiratory volume in 1 second, 6MST = six-minute stepper test.

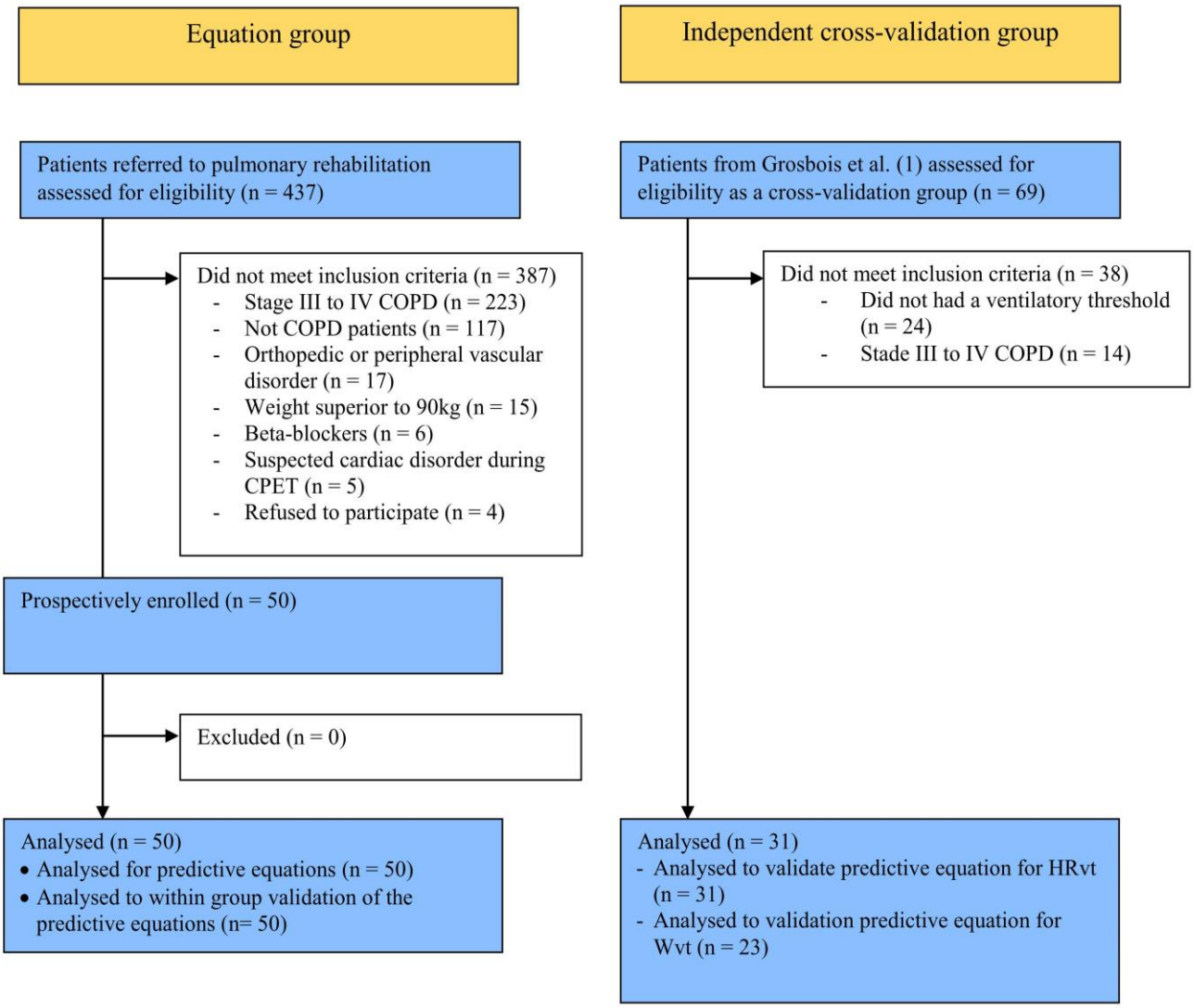
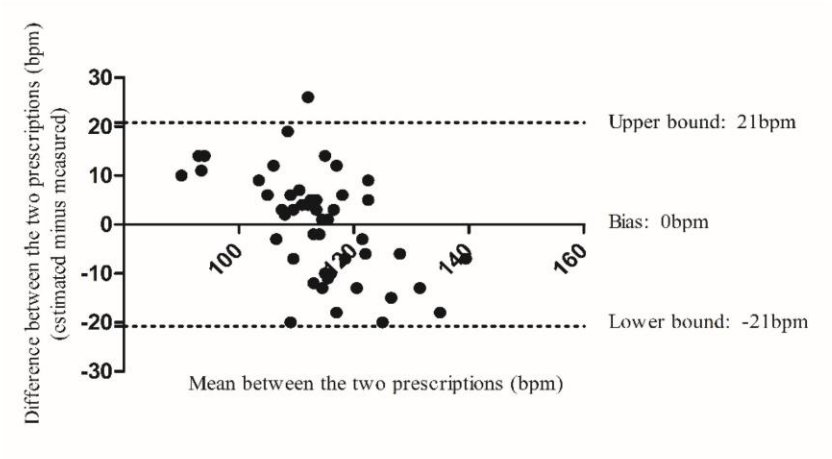


Figure 1: Flow chart.

COPD = chronic obstructive pulmonary disease, CPET = cardiopulmonary exercise testing, HRvt = heart rate at the ventilatory threshold during the CPET, Wvt = workload achieved at the ventilatory threshold during the CPET.

1. Grosbois JM, Riquier C, Chehere B, Coquart J, Behal H, Bart F, et al. Six-minute stepper test: a valid clinical exercise tolerance test for COPD patients. Int J Chron Obstruct Pulmon Dis. 2016;11:657-63.

A.



B.

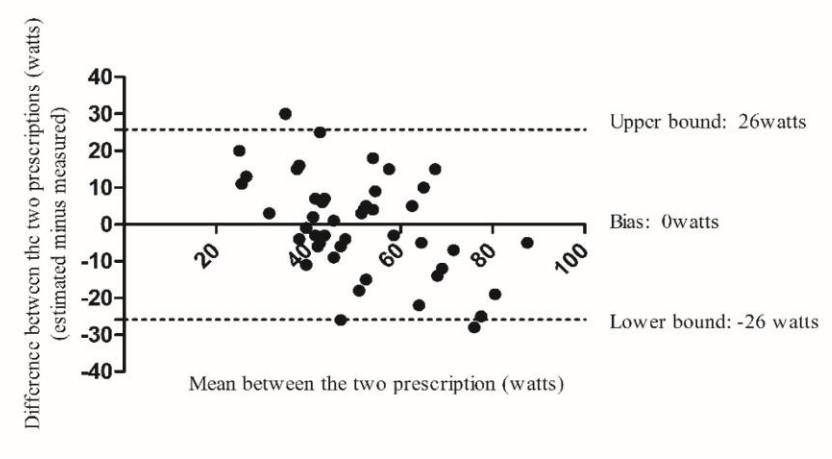


Figure 2: Bland-Altman plots for the prescription of HRvt within the equation group (A) and the prescription of Wvt within the equation group (B) using the predictive equations derived from the six-minute stepper test. The point-to-point difference between the two prescriptions (estimated minus actually measured) is plotted against the mean of the two prescriptions.

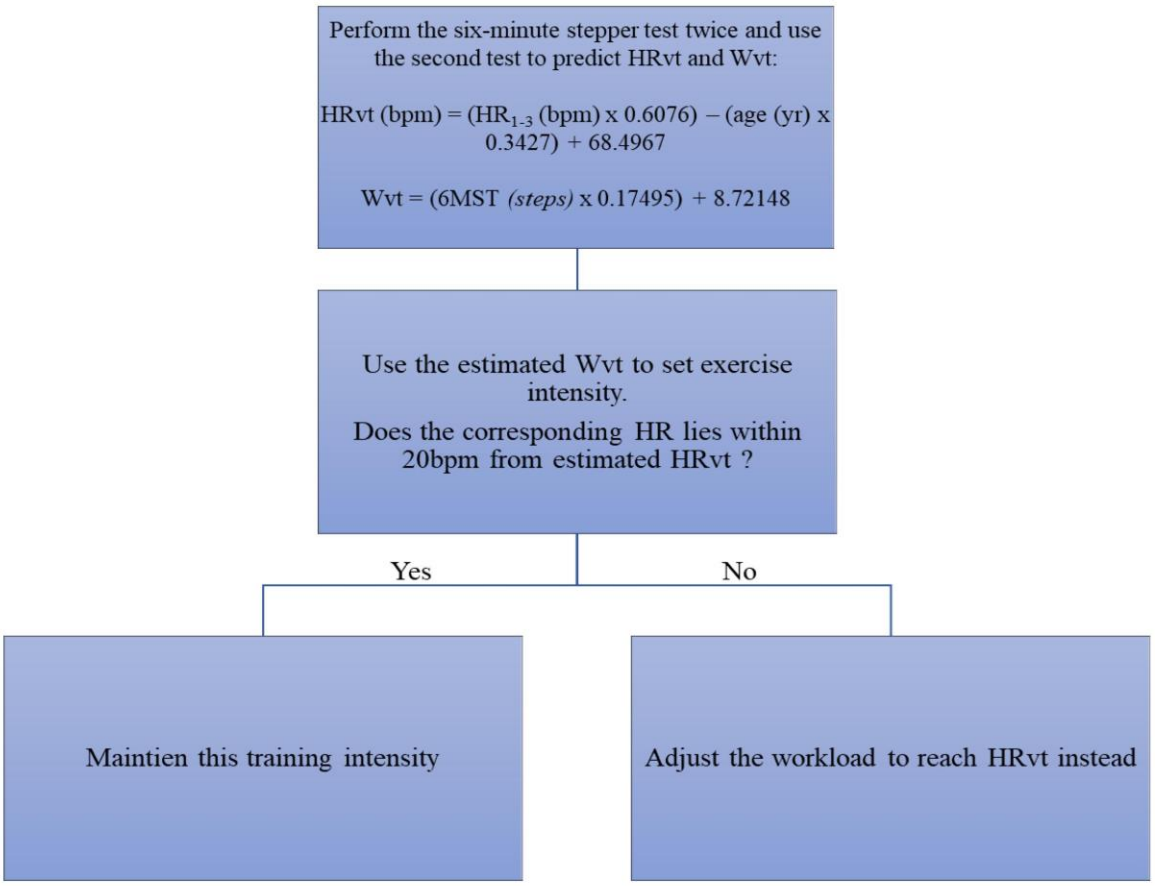
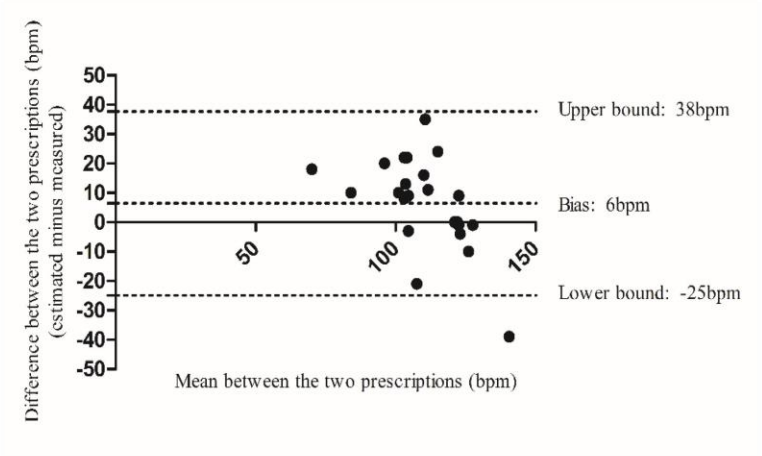


Figure 2: Algorithm to set training intensity according to the six-minute stepper test for people with early stage COPD.

HRvt = heart rate at the ventilatory threshold, Wvt = workload at the ventilatory threshold, HR_{1-3} = mean heart during the first 3 minutes of the six-minute stepper test.

A.



B.

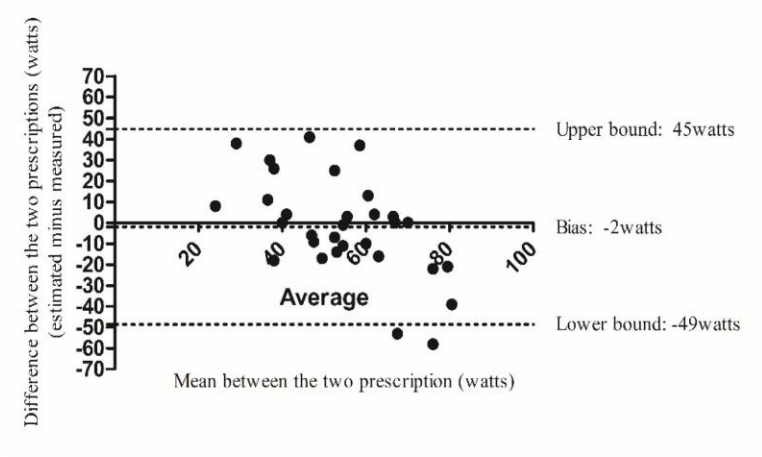


Figure S1: Bland-Altman plots for the prescription of HRvt within the cross-validation group (A) and the prescription of Wvt within the cross-validation group (B) using the predictive equations derived from the six-minute stepper test. The point-to-point difference between the two prescriptions (estimated minus actually measured) is plotted against the mean of the two prescriptions.

Table S1. Univariate relationship between HRvt, Wvt and covariates.

Covariates	Dependent variable			
	HRvt (n = 50)		Wvt (n = 50)	
	r	*p*	*r*	*p*
Gender	0.16	0.27	**0.34**	**0.01**
Age *(yr)*	**-0.30**	**0.04**	-0.15	0.31
Body mass index *(kg/m²)*	-0.08	0.60	0.19	0.18
HR_{1-3} *(bpm)*	**0.56**	**< 0.01**	Not assessed	
HR_{4-6} *(bpm)*	**0.49**	**< 0.01**	Not assessed	
Dyspnea *(Borg)*	0.15	0.29	-0.15	0.30
Fatigue *(Borg)*	**-0.24**	**0.10**	**-0.25**	**0.08**
FEV1 *(L)*, mean (SD)	0.07	0.62	**0.35**	**0.01**
6MST *(steps)*	Not assessed		**0.70**	**<0.01**

Pearson correlation test or logistic regression.

HRvt = heart rate at the ventilatory threshold, Wvt = workload at the ventilatory threshold, HR_{1-3} = mean heart during the first 3 minutes of the six-minute stepper test, HR_{4-6} = mean heart rate during the last 3 minutes of the six-minute stepper test, FEV1 = forced expiratory volume in 1 second, 6MST = six-minute stepper test.

Appendix.

Can the six-minute stepper test be used to determine the intensity of endurance training in early stage COPD: A multicenter observational study

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Appendix 1: Assessment.

Cardiopulmonary exercise testing: CPET was performed on an electromagnetic ergometer (Xercise, Cardiowise GmbH, Pirmasens, Germany). Following a 3 minutes warm-up period, incremental ramp exercise (5-20W/min) was applied up to exhaustion. A face mask (Hans Hudolph, Inc., Kansas city, MO), pneumotach, and gaz analyzer (Vyntus CPX, Care Fusion, San Diego, CA) were used to measure gases (oxygen consumption and carbon dioxide production) breath by breath [1]. The ventilatory threshold was manually derived as the average of 4 methods: first break in the minute ventilation curve, raise in the minute ventilation to oxygen consumption ratio without modification of the minute ventilation to carbon dioxide production ratio, raise in the end-tidal expired carbon dioxide gas and the Beaver's method [1,2]).

Six-minute stepper test: Participants performed two 6MSTs (Athlitec, Sassenage, France) as previously described [3-6]. The second test, which was used for analysis, began when the HR, and the transcutaneous oxygen saturation (SpO2) values returned to baseline values after a rest period of at least 20 minutes. The performance of the second test was recorded for analysis. HR and SpO2 were continuously recorded by pulse oximetry (WristOx2 pulse oximeter, model 3150, Nonin Medical Inc., Plymouth, MN) and then extracted using Nvision software (Henrotch, Aartselaar, Belgium). For the cross-validation group, punctual measurement was performed every minute.

Pulmonary function: Pulmonary function testing was performed according to the European Respiratory Society guideline and expressed as percentages of established theoretical values for European populations [7].

Appendix 2: Sample size calculation and statistical analysis.

Sample size calculation

According to VanVoorhis et al. [8], an absolute minimum of 10 participants per predictor variable is deemed appropriate. Therefore, we a priori planned to include 80 participants considering the following covariates: mean HR during the first (HR_{1-3}) or last (HR_{4-6}) 3 minutes of the 6MST, dyspnea and lower limb fatigue during the 6MST, age, weight, height, gender and FEV1. Due to difficulties in recruiting people with early-stage COPD, we prematurely stopped the study when reaching 50 participants and combined weight and height as body mass index (BMI) to limit analysis to the minimum.

Statistical analysis

The normality of the distribution was assessed using the Kolmogorov–Smirnov test and the D'Agostino & Pearson omnibus normality test. Categorical data were expressed as counts (%) and continuous data were expressed as mean (SD) or median (25th–75th percentile) according to the distribution. Baseline characteristics of both groups were compared with Fisher's test (for proportion) and independent Student's t-test or Mann–Whitney test (for continuous data), depending on the distribution. Specific analysis for the determination of the predictive equations as well as their validation are shown in Appendix 1.

A p-value <0.05 was considered statistically significant in all cases. GraphPad Prism 5.03 and R 3.6.1 softwares were used for analyses.

Determination of the predictive equations

In order to predict the HRvt, a multiple regression was undertaken using HRvt as the dependent variable. The relationship between the HRvt and the prespecified potential covariates (see *sample size calculation*) was assessed using univariate relationship (Pearson correlation test for continuous data and logistic regression for gender). Those variables related with HRvt with a p-value <0.10 were assessed for inter relationship and were entered in a multivariate analysis. In the case of a high inter relationship (r>0.80), only the variable the most related with HRvt was used.

Finally, a multivariate forward/backward stepwise regression was used to derive the best model to predict HRvt. The same procedure was applied to predict Wvt using the number of steps performed during the 6MST instead of HR_{1-3} or HR_{4-6}.

Validation of the predictive equation

The comparison of the prescribed intensities between the actually measured and estimated HRvt and Wvt at the group level were assessed using an independent Student's t-test and the mean absolute difference (MAD) [9]. The comparison at the individual level between both prescriptions was performed using a Bland-Altman analysis. Prescriptions were a priori considered to be clinically equivalent from a pragmatic point of view if the difference between prescriptions were not significantly different and if the 95% CI of the MAD lied within +/-10bpm for HRvt and +/- 14watts for Wvt. In addition, to ensure that the initial exercise prescription would not exceed the maximal HR achieved during the CPET for safety issue, the proportion of subjects for whom the predicted HRvt was higher than the maximal HR achieved during the CPET was assessed.

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Étude n°3

Utilisation du test stepper de 6 minutes pour prescrire le renforcement musculaire chez des patients atteints de BPCO – Une étude rétrospective

The six-minute stepper test is related to muscle strength but cannot substitute for the one repetition maximum to prescribe strength training in patients with COPD

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ORIGINAL RESEARCH

The six-minute stepper test is related to muscle strength but cannot substitute for the one repetition maximum to prescribe strength training in patients with COPD

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International Journal of COPD

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Purpose: There are many barriers to pulmonary rehabilitation, including a limited access to evaluation centers. To cope with these difficulties, field tests are often used to prescribe endurance training. As field tests are related to muscle strength, they could also be used to prescribe strength training and increase the access to pulmonary rehabilitation in rural area. However, their validity for this purpose has never been studied.

Patients and methods: The relationship between the 6-minute stepper test (6MST), 6-minute walk test, maximal workload achieved during cardiopulmonary exercise testing (Wpeak), and one repetition maximum (1RM) was assessed in 35 patients with COPD through a retrospective chart review to derive predictive equation of the 1RM from these tests. The effectiveness of these equations to prescribe strength training at 70% of the 1RM was assessed in an independent cross-validation group of 34 patients with COPD.

Results: There was a moderate relationship between the 6MST, Wpeak and the 1RM (r=0.44 and r=0.41, respectively, both $P \leq 0.01$). Whatever the test, the prescription of strength training using the estimated 1RM compared with the measured 1RM resulted in a mean absolute difference and a mean bias of about 30 kg.

Conclusion: The use of the 6MST and Wpeak for the prescription of strength training would result in a clinically not acceptable error. Therefore, they should not be used as a substitute for the 1RM to prescribe strength training.

Keywords: six-minute stepper test, strength training, COPD, pulmonary rehabilitation

Introduction

COPD is a worldwide cause of morbidity and mortality with a gradually increasing prevalence.[1,2] Pulmonary rehabilitation is widely recommended to cope with the systemic effects of COPD[3–5] and effectively improves exercise capacity and quality of life.[6] Unfortunately, <1% of patients who would benefit from it can access these programs, mainly due to the lack of rehabilitation and assessment centers, and their location in urban area. Pulmonary rehabilitation usually includes both endurance and strength training.[3–5] Thus, although the optimal assessment for endurance training prescription should include cardiopulmonary exercise testing (CPET),[3] it is often not available for a large number of patients. Alternatively, the one-repetition maximum (1RMw, which is the weight that can be lifted, pushed, or pulled only once without compensation) is

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frequently used in clinical practice for assessing and prescribing muscle strength.[4,9–11] However, it requires trained personnel and a learning period before the measurement to increase reliability and reduce bias, and is therefore time consuming. Moreover, it is possibly traumatic in several pathologies with comorbidities such as COPD (eg, bone, ligament, and muscular stress or injury).[10] Therefore, it can be difficult to obtain due to pain or muscle fatigue even though sub-maximal strength training (about 70% of 1RM as usually prescribed)[4,12–15] will be possible, highlighting a need for an easier and faster tool to assess and prescribe strength training.

Field tests have been proposed to replace CPET for the prescription of endurance training.[16–21] For example, the 6-minute stepper test (6MST), which is easier to perform than the widely used 6-minute walk test (6MWT) and does not need a 30 m long corridor,[22] has been validated to assess exercise capacity in patients with COPD[23–25] and has recently been considered for endurance training prescription.[17,20,21] Although field tests are often related to quadriceps muscular strength,[26–28] their use for strength training prescription has not been studied.

The aim of this study was to assess whether the 6MST could be used to prescribe strength training in patients with COPD accurately. The usability of the maximal workload attained during the CPET (Wpeak) and the 6MWT was also studied.

Materials and methods

Study design and patient selection

Patients with COPD referred for pulmonary rehabilitation between September 2015 and October 2018 to the ADIR Association (Association d'aide à domicile des patients insuffisants respiratoires), Rouen University Hospital, France, were retrospectively studied. The study was approved by the Comité d'Ethique de la Recherche non-interventionnelle from Rouen University Hospital (E2018-67). According to the French law, patients were informed in writing that their data could be used for future research purposes and formal consent to retrospectively review their medical records was not required. None of these patients used this right of refusal. Patient data confidentiality was maintained and the protocol was performed in compliance with the Declaration of Helsinki.

Inclusion criteria

Patients with a clinical diagnosis of COPD (FEV_1/FVC ratio <0.70) were included. The severity of airflow limitation was assessed according to the GOLD classification.[29] They had to be 18 years old; stable (free from acute exacerbation in the previous month); and have performed both the 6MST and the quadriceps 1RM assessment during the first session of their pulmonary rehabilitation. They also had to weigh 90 kg or less (maximum weight supported by the stepper).

Exclusion criteria

Patients for whom the quadriceps 1RM exceeded 120 kg on one limb (leg press's limit) and those for whom the 1RM was not maximal due to musculoskeletal limitation were excluded.

Data extraction

Data regarding demographic features, comorbidities, pulmonary function, exercise capacity (6MST, Wpeak, and 6MWT), quadriceps 1RM, and use of long-term oxygen or home mechanical ventilation were extracted though a retrospective chart review.

Assessment

1RM

Quadriceps 1RM was performed on a pulley press (Legpress; Design Corporel, Salomé, France). Patients were in a semi-sitting position, back against the backside with a 90° knee and hip flexion.[30] They were vigorously encouraged to extend both of their knees simultaneously. Patients had to put their hands on the side handles of the press or to keep them on their stomach. In the case of values exceeding 120 kg divided over the two lower limbs, the press reached its limit. Therefore, the search for the 1RM value proceeded as before: with a progressive rise in the weight if the lift was successful, however it was now realized on the one leg. Therefore, patients were told to put the foot of the exercising lower limb in the middle of the steel plate and the other lower limb (not exercising) on the sliding rail in order to avoid any compensation. The sum of both lower limbs was considered as quadriceps 1RM.

6MST

Patients performed two 6MSTs (Athlitec; GoSport, Sassenage, France). The second test began when the heart rate (HR), and the transcutaneous oxygen saturation (SpO_2) values returned to baseline values after a rest period of at least 20 minutes. The performance of the second test was recorded for analysis.[20] Standardized instructions were based on the American Thoracic Society guidelines for the 6MST as previously described.[23]

CPET

CPET was performed on an electromagnetic braked ergometer (Ergoselect 200; Ergoline, Bitz, Germany).

Following a 3 minutes warm-up period, incremental ramp exercise (5–20 W/min) was applied up to exhaustion. A pneumotachograph and a gas analyzer (Ergocard; Medisoft, Louvain, Belgium) were used to measure gases (oxygen consumption [VO_2] and carbon dioxide production [VCO_2] breath by breath) through a face mask (Hans Rudolph, Inc., Kansas City, MO, USA). The last ramp maintained before exhaustion or the workload achieved at VO_2peak was considered as Wpeak.

6MWT

The 6MWT was performed according to the American Thoracic Society guidelines along a 30 m corridor.[22] The test was carried out twice and the longest distance was used in the analysis.

Outcome

The evaluation of the reliability of using the 6MST to prescribe the strength training involved four steps. First, the relation between the number of steps performed during the 6MST and the quadriceps 1RM was assessed in the first group of subjects (prediction group) with COPD.[31] Next, in the case of a significant relationship, a linear regression was performed to derive a predictive equation of the 1RM from the 6MST. Third, in a second and independent cross-validation group of subjects with COPD, the quadriceps 1RM was estimated from the predictive equation. The last step was to assess the error that would be associated with using estimated 1RM to prescribe strength training in a clinical situation (70% of the 1RM).[4,12–15] The same method was applied for both Wpeak and the 6MST.

Statistical analysis

The normality of the distribution was assessed using the Kolmogorov–Smirnov test. Categorical data were expressed as counts (%) and continuous data were expressed as mean (SD) or median (25th–75th percentile) according to the distribution. Comparison between the baseline characteristics of both groups was assessed with Fisher's test (for proportion) and independent Student's *t*-test or Mann–Whitney test, depending on the distribution.

Determination of the predictive equation in the prediction group

The relationship between the 6MST, Wpeak, 6MWT, and 1RM was assessed using Pearson or Spearman correlation test. Single linear regressions were performed when appropriate. Since several data were not normally distributed, they were normalized using a log-transformation. A predictive equation using linear regression was then derived.

Validation of the predictive equation in cross-validation group

The comparison of the prescribed workload (70% 1RM) between the measured 1RM and the estimated 1RM was assessed using the mean absolute difference (MAD) between both prescription and a Bland–Altman analysis. As the increment of the leg press is done by 5 kg, the prescriptions were a priori considered as clinically equivalent if the limits of agreements (upper and lower bounds) were <5 kg. A P-value <0.05 was deemed significant. Prism 5 software was used for analyses.

Results

Patients

Among the 356 patients referred for pulmonary rehabilitation over the study period, 78 met the inclusion criteria. Two were excluded because the quadriceps 1RM exceeded 120 kg on one limb. A further seven were excluded from the analysis because the 1RM was limited due to musculoskeletal impairment (Figure 1). Finally, 69 patients were included for the analysis. The first 35 patients were selected to derive the predictive equations,[31] while the 34 subsequent patients were used to assess the validity of the equations to prescribe strength training (cross-validation group). The patients' characteristics of both groups are shown in Table 1. Overall, the mean age was 60 (SD 10) years, 42% were women, and 30% were long-term oxygen users. They had a severe obstruction (median FEV_1%: 38 [IQR 30–58]) and impaired

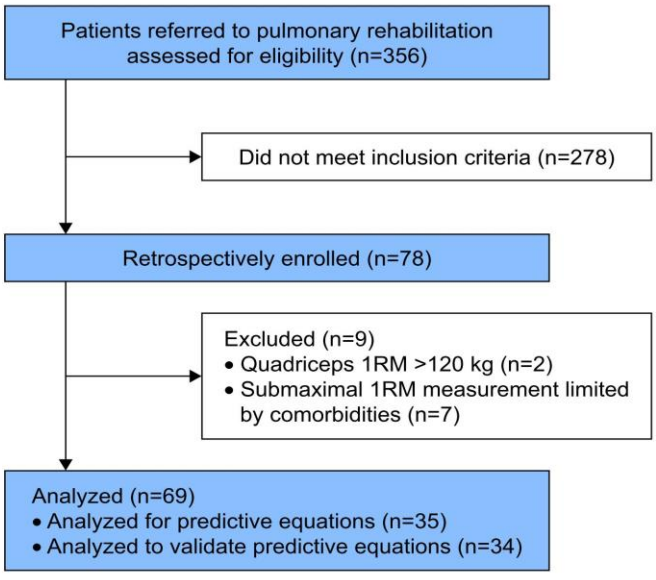

Figure 1 Flow of patients through the study.
Abbreviation: 1RM, one repetition maximum test.

Table 1 Characteristics of the patients

Characteristics	Patients		Between-group comparison
	Prediction group (n=35)	Cross-validation group (n=34)	*P*-value
Gender, n female (%)	10 (29)	19 (56)	**0.03**
Age (years), mean (SD)	61 (9)	59 (11)	0.40
Height (cm), mean (SD)	167 (8)	165 (9)	0.40
Body mass (kg), mean (SD)	61 (14)	64 (15)	0.54
Body mass index (kg/m²), mean (SD)	21.9 (4.1)	23.2 (4.7)	0.22
FEV_1 (L), median (IQR)	1.0 (0.7–1.6)	1.1 (0.8–1.7)	0.54
FEV_1 (%), median (IQR)	36 (26–58)	43 (32–59)	0.30
FVC (L), median (IQR)	2.6 (2.0–3.4)	2.5 (1.8–3.4)	0.63
FEV_1/FVC (%), mean (SD)	43 (12)	48 (13)	0.15
Residual volume to total lung capacity, mean (SD)	0.6 (0.1)	0.6 (0.1)	0.18
VO_2peak (mL/kg/min), mean (SD)	14 (3)	14 (4)	0.40
Wpeak (W), median (IQR)	70 (40–80)	50 (40–80)	0.72
6MST (steps), mean (SD)	195 (62)	190 (70)	0.74
6MWT distance (m), median (IQR)	451 (416–490)	420 (381–510)	0.64
Quadriceps 1RM (kg), median (IQR)	100 (90–140)	100 (84–153)	0.58
Long-term oxygen use, n (%)	13 (37)	8 (24)	0.30
Home mechanical ventilation use, n (%)	6 (17)	5 (15)	1.00
Comorbidities, n (%)			
Peripheral arterial disease, n (%)	4 (11)	0 (0)	0.11
Hypertension, n (%)	8 (23)	3 (9)	0.19
Hypercholesterolemia, n (%)	7 (20)	1 (3)	0.06
Diabetes, n (%)	3 (9)	1 (3)	0.61
Cardiopathies, n (%)	4 (11)	5 (15)	0.73
Lung cancer, n (%)	7 (20)	6 (18)	1.00

Notes: Percentages may not sum to 100 due to rounding. Fisher's test for categorial data, and Mann–Whitney or independent *t*-test for other characteristics. Bold values indicate statistical significance.

Abbreviations: VO_2peak, maximal oxygen consumption; 6MST, 6-minute stepper test; 6MWT, 6-minute walk test; 1RM, one repetition maximum test; Wpeak, maximal workload achieved during cardiopulmonary exercise testing.

exercise capacity (mean VO_2peak: 14 [SD 4] mL/kg/min). There were significantly more females in the cross-validation group (56% compared with 29%, P=0.03).

Relationship with the 1RM (prediction group)

There was a significant relationship between the 6MST, Wpeak and log1RM (r=0.44, P<0.01 and r=0.41, P=0.01, respectively, Figure 2A and B). The 6MWT was only available for 13 patients and there was no significant relationship with log1RM.

Predictive equations (prediction group)

Log1RM could be predicted, respectively, for the 6MST and Wpeak by the following equations (Figure 2A and B):

$$\text{Log1RM} = 0.0009379 \times \text{6MST (steps)} + 1.713;$$

$$\text{Log1RM} = 0.00223 \times \text{Wpeak (W)} + 1.757.$$

As the 6MWT was not correlated with log1RM, no predictive equation was derived.

Validation of the predictive equations (cross-validation group)

The MAD between the prescriptions of strength training at a value of 70% of the 1RM using the actually measured and the predicted 1RM was 31 (SD 30) kg for the 6MST and 29 (SD 28) kg for Wpeak. The limits of agreement and corresponding Bland–Altman plots are presented for the 6MST in Figure 3A and for Wpeak in Figure 3B.

Discussion

The main finding of this study was that there was a significant relationship between exercise capacity assessment tests used to prescribe endurance training and the 1RM. However, this relationship was only moderate, and the use

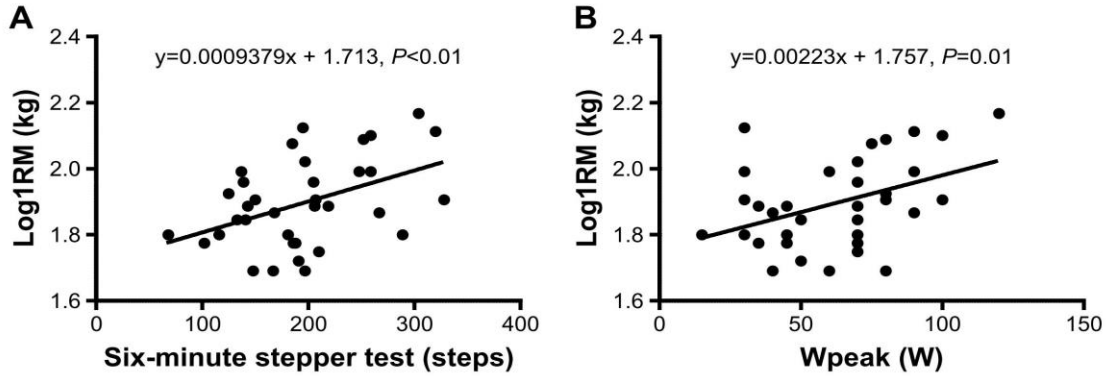

Figure 2 Linear relationship and predictive equations between (**A**) the 6-minute stepper test, (**B**) the maximal workload achieved during the cardiopulmonary exercise testing (Wpeak) and the one repetition maximum (1RM).

of predictive equations to estimate the 1RM from these tests to prescribe strength training would result in an inacceptable error for clinical practice (about 30 kg). As can be seen in Figure 3A and B, the amount of error seems to increase with the increase of the 1RM.

The assessment of the 1RM is the gold standard for strength training prescription.[4,9] However, it could be compromised in pathological condition and is time consuming.[11] Although the measurement of the 1RM was found to be feasible in a small cohort of patients with COPD,[30] it might be limited by comorbidities. In the present study, about 10% of the patients were excluded due to pain (due to musculoskeletal comorbidities) during the measurement, which led to an underestimation of the 1RM even though strength training at 70% 1RM would have been possible. Therefore, indirect measurement of the 1RM to allow effective training seems necessary.

There are many barriers to pulmonary rehabilitation, including a limited access to evaluation centers and CPET.[7,8] To cope with these difficulties, field tests are often used to prescribe endurance training.[16–21] As several field tests are related to muscle strength,[26,27] as well as the 6MST in the present study, the idea to use the same test to prescribe both endurance and strength training looks attractive at the first glance to increase the access to pulmonary rehabilitation in rural area. Surprisingly, there was no relationship between the 6MWT and the 1RM. Conversely, Rausch-Osthoff et al found a significant moderate correlation between the quadriceps strength and the distance covered during 6MWT.[27] This difference was likely due to the few numbers of 6MWT records available in subjects from the prediction group because the study was not designed for this outcome.

However, the present results suggest that the use of both the 6MST and CPET to prescribe strength training would result in a significant error, refuting their use for clinical practice. In healthy subjects, several authors suggested the use of anthropologic data such as age, gender, height, weight, lean body mass, and thigh girth.[10] Adding these characteristics in a multivariate analysis in a larger cohort of subjects with COPD may help to refine the present equations and improve their

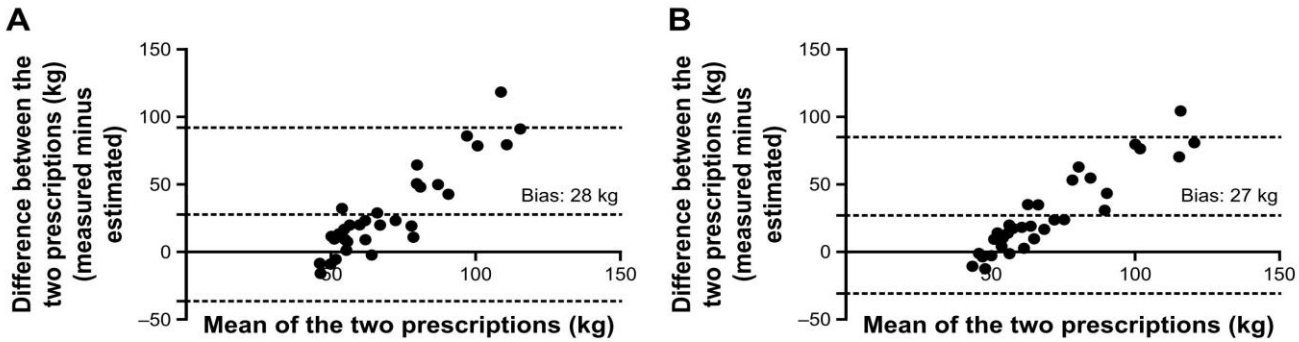

Figure 3 Bland–Altman plots for the prescription of strength training using the predictive equations derived from the 6-minute stepper test (**A**) and Wpeak (**B**). The point-to-point difference between the two prescriptions (actually measured minus estimated) is plotted against the mean of the two prescriptions. 95% CI limits of agreement (lower and upper bounds) were –36 to 92 for the 6MST and –31 to 85 for Wpeak.
Abbreviations: 6MST, 6-minute stepper test; Wpeak, the maximal workload achieved during the cardiopulmonary exercise testing.

accuracy to prescribe strength training. Alternatively, the prediction of the 1RM from the perceived exertion (BORG scale)[11,32] has been proposed for healthy subjects but remains to be evaluated in subjects with COPD.

There are several explanations for the inaccuracy that occurred when using the estimated 1RM to prescribe strength training.

First, the relationship between Wpeak, 6MST and the 1RM was only moderate (r=0.40). Since cycling, stepping, and strength training provide substantially different effort and metabolic load,[33–36] several parameters such as ventilatory pattern, hematosis, cardiovascular adaptation, muscle mass involved, weight, and balance may explain this moderate correlation. Moreover, compared with endurance capacity, muscular strength is relatively well preserved in patients with COPD due to a shift toward an increased proportion of fast twitch muscular fiber (type II), which are specifically recruited during strength training and the 1RM assessment.[37] Conversely, Wpeak and the 6MST do not only reflect the type II fibers activity but also include the recruitment of the slow twitch fibers (type I), as suggested by the relationship between the 6MST and VO_2peak.[25] This may also contribute to explain the systematic bias observed in the Bland and Altman analysis (Figure 3) showing that the error increases proportionally to the 1RM (eg, the least disabled patients had a preserved type II fibers and a high 1RM but likely an already present alteration of the type I fibers and therefore a relatively low performance on the 6MST). Additionally, the nature of the 1RM assessment and strength training allows the patients to rest between repetitions while the exercise is continuous during cycling or stepping, causing more dyspnea and fatigue in the latter.[36] This likely allowed a more important recruitment of muscular fibers during the assessment of the 1RM.

Secondly, there were significantly more females in the cross-validation group. This might have introduced some bias due to gender, since it has an impact on perceived dyspnea[38] and muscular type fibers.[39] However, the latter is reported inconsistently,[40] and there are no gender differences in cardiopulmonary responses during the 1RM testing.[30] Therefore, it is unlikely that these factors alone account for the amount of error observed between both prescriptions.

Limits and strength

First, a bias cannot be excluded due to the retrospective design of the study. However, this reflected daily clinical practice providing external validity of the results. Moreover, statistical tests were limited to those reported in order to avoid any type one error due to multiple comparison frequently encountered in retrospective studies. Secondly, the population was relatively selected (eg, no major balance impairment and weight under 90 kg for the 6MST). This cannot be neglected considering that a considerable number of patients with COPD are overweight[41,42] and present balance disorders.[43]

The most important strength of this study was the evaluation of the predictive equation in an independent cross-validation group which has invalidated the use of both tests for the prescription of strength training.

Conclusion

Wpeak and the 6MST are both related to the quadriceps strength (1RM). Although the CPET and the 6MST could be used to prescribe endurance training in patients with COPD, their use for the prescription of strength training would result in a clinically nonacceptable error. Therefore, they should not be used for this purpose and both the 1RM and the voluntary maximal contraction remain the recommended methods to assess muscle strength in clinical practice. Further prospective studies are needed to confirm these results and explore the potential usefulness of the 6MWT for this purpose.

Ethics approval

This study was approved by the Comité d'Ethique de la Recherche non-interventionnelle from Rouen University Hospital (E2018-67).

Data sharing statement

Deidentified participant data published in the manuscript will be shared to searchers performing a meta-analysis on request. Data will be available after publication.

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Disclosure

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I.4. Faisabilité, validité et acceptabilité d'un outil de telemonitoring

Afin de faire face au manque de places disponibles dans les centres de réhabilitation respiratoire et aux difficultés de transport pour s'y rendre, la réhabilitation respiratoire en secteur libéral (kinésithérapeute de ville) ou à domicile a été proposée depuis plusieurs années. De récentes méta-analyses ont démontré que ces modalités pouvaient être une alternative efficace aux programmes de réhabilitation réalisés plus traditionnellement en hospitalisation ou en ambulatoire dans des centres spécialisés (74-76). Cependant, lorsque la réhabilitation est réalisée à domicile, l'utilisation des technologies de santé s'avère nécessaire afin de toucher un nombre important de participants de façon efficace tout en permettant une supervision équivalente à celle proposée en centre ou en cabinet de kinésithérapie libéral (feedback direct, rapide ou automatique pour individualiser l'entrainement ; monitorage des paramètres cardiorespiratoires au cours de l'effort pour des raisons des sécurité (77, 78) ; évaluation de l'adhérence au programme pour générer des alertes de contact ou stimuler l'exercice autonome (79)) : on évoque alors les termes de telemonitoring ou télé réhabilitation (77, 78, 80-87). Bien que les patients adressés en réhabilitation aient un engagement substantiel avec les nouvelles technologies (88), la validité de la transmission à distance de données de fréquence cardiaque et de saturation transcutanée en oxygène n'a jamais été comparée à des données mesurées directement chez des patients avec un handicap ventilatoire. Des recherches menées chez des sujets sains ont montré que les données et leurs précisions pouvaient être influencées par le réseau de transmission et le système de télésanté utilisé, causant environ 20% d'artefacts (89). D'autre part, les questions de faisabilité de l'utilisation de ces technologies par les patients et de leur satisfaction vis-à-vis de ces dispositifs se posent. L'objectif de la contribution originale présentée ci-dessous est donc d'évaluer la faisabilité, la validité et l'acceptabilité d'un outil de telemonitoring.

Étude n°4

Faisabilité, validité et acceptabilité d'un outil de telemonitoring pour la réalisation de la réhabilitation à domicile

People undertaking pulmonary rehabilitation are willing and able to provide accurate data via a remote pulse oximetry system: a multicentre observational study

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Research

People undertaking pulmonary rehabilitation are willing and able to provide accurate data via a remote pulse oximetry system: a multicentre observational study

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KEY WORDS

Pulmonary rehabilitation
Telemonitoring
Telerehabilitation
Exercise
Physical therapy

ABSTRACT

Questions: Can people referred to pulmonary rehabilitation easily learn to use a system for remote transmission of oximetry data? Do they consider remote transmission of oximetry data to be satisfactory? Are the transmitted data valid compared with locally stored data? **Design**: Multicentre, prospective, observational study. **Participants**: One hundred and five adults with chronic respiratory disease who were referred to pulmonary rehabilitation. **Intervention**: At an initial session, participants were taught to record and transmit their oximetry data to a remote server. At subsequent testing session(s), participants were requested to independently activate and use the oximetry monitoring system for a period of exercise on a cycle ergometer, until autonomy with the system was demonstrated. A subgroup of five participants undertook five 45-minute training sessions to generate a dataset to assess whether the transmitted data were valid compared with the locally stored data. **Outcome measures**: Outcome measures included the number of sessions needed to become autonomous, participant satisfaction with the system, and measures of the validity of the transmitted data. **Results**: Participants became autonomous quickly: 86% at the first testing session and 100% within three testing sessions. At least 98% of participants agreed that the system was easy to use and they would be willing to use it throughout pulmonary rehabilitation. The system transmitted usable data from 98% (95% CI 96 to 100) of sessions and introduced minimal artefact. Mean absolute differences were 0.365 beats/minute for heart rate and 0.133% for oxyhaemoglobin saturation. For heart rate, exact agreement was 72% (SD 9) and similar agreement (within 3 beats/minute) was 99% (SD 1). For oxyhaemoglobin saturation, exact agreement was 87% (SD 3) and similar agreement (within 3%) was 100% (SD 0). **Conclusion**: The telemonitoring system used in this study was sufficiently valid and acceptable for use in at-home pulmonary rehabilitation by people with chronic respiratory disease. **Study registration**: ClinicalTrials.gov NCT03295474 and NCT03004716 (subgroup study). **[Bonnevie T, Gravier F-E, Elkins M, Dupuis J, Prieur G, Combret Y, Viacroze C, Debeaumont D, Robleda-Quesada A, Quieffin J, Lamia B, Patout M, Cuvelier A, Muir J-F, Medrinal C, Tardif C (2019) People undertaking pulmonary rehabilitation are willing and able to provide accurate data via a remote pulse oximetry system: a multicentre observational study. *Journal of Physiotherapy* 65:28–36]**

Introduction

Chronic respiratory disease is a leading cause of disability and mortality.[1,2] For example, chronic obstructive pulmonary disease (COPD) is the fifth leading cause of death worldwide and its prevalence is increasing gradually.[3] The respiratory symptoms are progressive and lead to physical inactivity and muscle wasting, resulting in a spiral of worsening dyspnoea and deconditioning.[4] Asthma

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caused 0.4 million deaths in 2015.[5] Together, these diseases account for 3.7% of global disability-adjusted life years,[5] which is a measure of overall disease burden.

Pulmonary rehabilitation was developed to counteract the systemic effects of chronic respiratory disease. For people with COPD, it reduces dyspnoea, lowers the risk of hospital readmission after acute exacerbation, and improves exercise capacity and quality of life.[6,7] It has similar benefits in other chronic respiratory diseases.[8] Unfortunately, access to pulmonary rehabilitation is limited for many people who would benefit from it, primarily because of environmental factors such as waiting times, limited number of programs, and urban location of the programs.[9] Thus, despite widespread recommendations that people with COPD attend these programs,[10–12] $<$ 1% of people with COPD access these programs.[13–15]

Delivering pulmonary rehabilitation in the patient's home is effective[16,17] and may help to prolong its benefits.[18] However, home-based pulmonary rehabilitation will only be able to reach large numbers of participants efficiently and provide the peer support that centre-based pulmonary rehabilitation provides if it uses new technologies to allow the physiotherapist to remotely link participants in a virtual class format. Several studies have suggested that this 'telerehabilitation' form of pulmonary rehabilitation safely improves physical capacity and quality of life[19–27] and lowers the risk of hospitalisation.[28]

For the day-to-day operation of telerehabilitation, participants will need to engage with new technologies to some extent. Some form of audiovisual remote communication technology will be required, at least with a link between each patient and the clinician, but potentially with videoconferencing to facilitate peer-to-peer contact. Despite being an older population, the majority of people with chronic respiratory disease attending a pulmonary rehabilitation program have substantial engagement with technology: 92% regularly use a technological device such as a smartphone or tablet; 60% are willing to use telerehabilitation; and 57% rate their technological skills as adequate, good or very good.[29] While this is encouraging, some telerehabilitation programs do (and arguably all should) go beyond simple audiovisual remote communication and incorporate remote monitoring of heart rate (HR) and transcutaneous oxygen saturation (SpO_2) through wireless oximeters.[23,26] Monitoring of HR and SpO_2 is recommended in the Pulmonary Rehabilitation Toolkit (www.pulmonaryrehab.com.au) for safety (including determination of contraindications to exercise and the need for supplemental oxygen) and to determine the patient's physiological response to exercise, which may assist prescription and progression. However, remotely transmitted HR and SpO_2 data have not been compared with data from direct measurements in patients with respiratory disease. Research involving healthy participants has shown that the data and their accuracy could be influenced by the transmission network and the telehealth system, causing about 20% artefacts.[30] Furthermore, there has not been adequate investigation into whether people referred to pulmonary rehabilitation are able to use such a transmission system and whether they find it satisfactory.

Therefore, the main research questions for this observational study were:

1. Can people referred to pulmonary rehabilitation easily learn to use a system for remote transmission of oximetry data?
2. Do people referred to pulmonary rehabilitation consider remote transmission of oximetry data to be satisfactory?
3. Are the transmitted data valid compared with locally stored data?

Method

Design

This was a multicentre, prospective, observational study. People who were referred to pulmonary rehabilitation were recruited. Before commencing the program, they underwent some baseline assessments and were taught to use a system for recording and transmitting their pulse oximetry data. Each participant then undertook a prescribed exercise session on a cycle ergometer with the oximeter in situ. At a subsequent session, participants were requested to independently activate and use the oximetry monitoring system for another cycling session. If they did not successfully transmit the data, the instructions were repeated and subsequent sessions were undertaken until they were successful. Participants were questioned about their satisfaction with the system. A subgroup of participants undertook five 45-minute exercise sessions over 10 days with their oximetry data recorded locally and also transmitted to a remote server using the same system. These recordings were used to test the validity of the transmitted data against the directly recorded data.

Participants, therapists, centres

Between January 2017 and April 2018, adults with chronic respiratory disease referred to pulmonary rehabilitation at ADIR Association, Rouen University Hospital, France and Jacques Monod Hospital, Le Havre, France were approached consecutively and assessed for eligibility. Those who were deemed eligible were invited to participate in the study. Chronic lung disease and referral to pulmonary rehabilitation were the only inclusion criteria, with no restriction on the type of chronic respiratory disease. Exclusion criteria were (potential) pregnancy, guardianship, refusal to consent, and contraindication to pulmonary rehabilitation. The two participating centres were tertiary referral hospitals with pulmonary rehabilitation programs that typically manage between 150 and 200 patients per year with staffing by physiotherapists.

Data collection

Baseline assessment

Before starting the pulmonary rehabilitation program, each participant underwent a comprehensive assessment according to current guidelines, including pulmonary function tests,[31] a 6-minute walk test (the test was carried out twice and the longest distance was used in the analysis),[32,33] and a cardiopulmonary exercise test.[34] Demographic data, gender, body mass index, disease, disease severity, and comorbidities were also recorded.

Telemonitoring system

The monitoring system consisted of a Bluetooth pulse oximeter[a] that recorded heart rate and SpO_2 at a frequency of 1 Hz. This information was saved into a database stored locally on a computer, constituting Database 1. At the same time, the data were transmitted to an acquisition and transmission device[b] and sent over the Global System for Mobile communications (GSM) to a remote monitoring platform[c] outside the hospital. These data were stored in Database 2 on a remote secure server. The recordings were then retrieved and downloaded by the therapist for comparison with the local data extracted from the oximeter (Figure 1). (A photograph of the oximeter in situ is presented in Figure 2 on the eAddenda.)

Familiarisation with the telemonitoring system

After enrolment, an investigator physiotherapist taught the participants how to use the telemonitoring system, which involved four steps. First, the participants attached the oximeter[a] to their wrists and applied the sensor to their index fingers. Next, they pushed the Bluetooth button on the bottom of the oximeter[a], and then pushed a large button on the bottom of the transmission device to initiate synchronisation. The final step was to verify the effectiveness of the transmission by means of a flashing light on the transmission device[b]. Participants were instructed to repeat the procedure if the light was not flashing. No other type of teaching or support was given (eg, written materials). The teaching time lasted $<$ 5 minutes. Thereafter, the participants performed a cycling session according to their prescription.

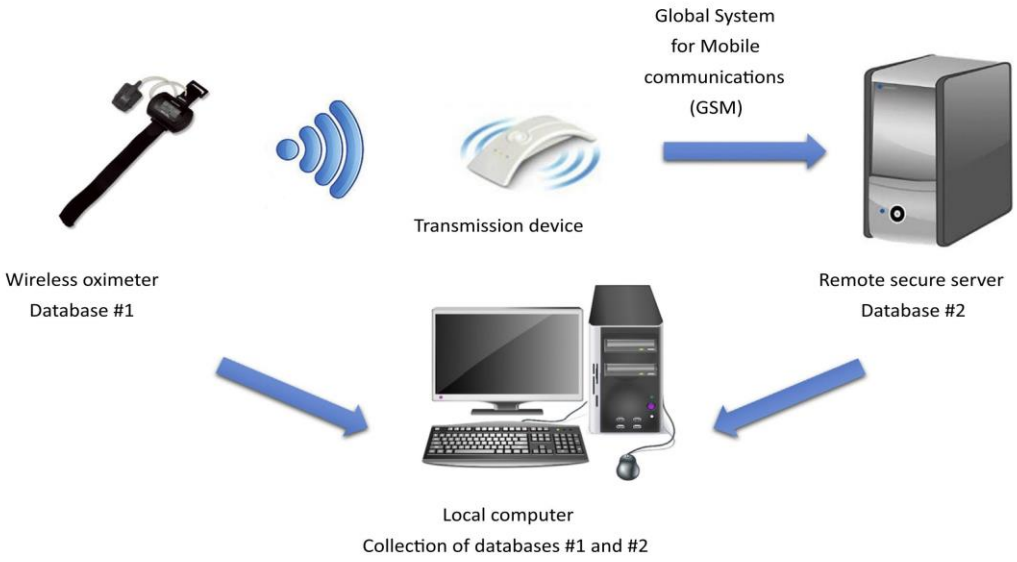

Figure 1. Hardware components of the telerehabilitation platform.

Usability of the telemonitoring system

Subsequent sessions were scheduled to determine when the participants became autonomous with transmitting their data via the telemonitoring system. At the start of each of these sessions, no further instruction was given to the participants. The participants applied the oximeter and activated the system autonomously to begin transmission of data. The participants were advised only to carry out the cycling session when they believed that they had successfully applied and activated the device. In case of error, the therapist stopped the session and repeated the instruction about the four steps. In this event, the participant was considered not autonomous and a new session of evaluation was scheduled. In case of success, the participant was considered autonomous and no further assessment sessions were scheduled. In order to be sure that the device worked correctly, the therapist connected to the remote monitoring platform[c] server to be sure that a dataset was transmitted. If the participant was still not autonomous after the fifth session, the protocol ended and the participant was considered to be not autonomous at the end of the study. The number of sessions needed for each participant to become autonomous in the use of the device was tallied.

Satisfaction with the telemonitoring system

At each session, participants rated the equipment's ease of use, their willingness to use it for pulmonary rehabilitation, and their overall satisfaction with the equipment. The satisfaction scale was developed based on expert opinion. These ratings were recorded using 4-point Likert-type scales (Box 1).

Validity of the telemonitored data

The five first participants included in the study formed a subgroup that participated in five 45-minute exercise sessions, each at least 24 hours apart, over a period of 10 days. Sessions were continuously monitored with the telemonitoring device, allowing direct comparison of the data stored on Database 1 and Database 2. At this stage, measurements were performed by the investigator physiotherapist for the initiation session and according to the participant's autonomy for the subsequent sessions. Moreover, the rate of data successfully retrieved from the transmission device[b] server was calculated as the number of sessions successfully retrieved divided by the total number of sessions performed.

Data analysis

The normality of the distribution of each variable was assessed using the Kolmogorov Smirnov test. Categorical data were expressed as counts (%). Continuous data were expressed as means (SD) or medians (IQR), depending on the distribution. To determine the precision of some estimates, 95% CIs were calculated.

Ability to record and transmit oximetry data autonomously

Descriptive statistics were used to characterise the participants. The number of sessions required for participants to become able to record and transmit the data autonomously were also summarised descriptively. Unpaired *t*-tests or Mann-Whitney tests were used to compare the baseline characteristics of participants who were autonomous at the first session after initiation versus those who were not.

Satisfaction with the transmission system

The ratings of agreement with the statements in Box 1 were summarised graphically and with descriptive statistics. McNemar's test was used to assess the change (from the teaching session to the first autonomous session) in the proportion of participants who gave ratings of 'strongly agree' or 'very satisfied' in response to the statements in Box 1.

Box 1. English translation of the questions used to rate the participants' satisfaction with the remote oximetry monitoring system.

Please rate your level of agreement with this statement:

This equipment is easy to use.

- strongly disagree
- disagree
- agree
- strongly agree

Please rate your level of agreement with this statement:

I would be willing to carry out my entire pulmonary rehabilitation program with this equipment.

- strongly disagree
- disagree
- agree
- strongly agree

Overall, how satisfied are you with this equipment?

- strongly dissatisfied
- dissatisfied
- satisfied
- very satisfied

Validity of the transmitted data

Several methods were used to compare the data in Databases 1 and 2. These included the percentage of usable data, mean absolute difference, percentage exact agreement, percentage similar agreement, and the Bland and Altman limits of agreement method.

The percentage of usable data was calculated by removing the data identified as measurement artefacts from Database 1 and Database 2 and comparing the number of remaining data points in Databases 1 and 2. Measurement artefacts were identified as values $>$ 250 beats/minute for HR and 100% for SpO_2.

The mean absolute difference was calculated as the mean of the magnitude of the difference (ie, the amount of error introduced by transmission) in paired data between Databases 1 and 2.

Percentage exact agreement was calculated based on the two values being identical. Percentage similar agreement was calculated based on SpO_2 values being within $\pm$ 3% (absolute) and within $\pm$ 3 beats/minute for HR. In the clinical experience of the authors, these thresholds were considered to represent acceptable error between the two data points. Furthermore, the threshold of 3% has also been used by other authors as an acceptable error for SpO_2 because it is adequate precision for determining hypoxaemia in remote monitoring,[35] and the threshold of 3 beats/minute for HR is equivalent to the accuracy of the device[a] according to the manufacturer.

The limits of agreement method enabled quantification of the agreement between the two databases. Specifically, it provided the upper and lower bounds with 95% CI (ie, mean $\pm$ 1.96 $\times$ SD). For this method, data were averaged every 10 seconds and the means were compared between databases.

Results

Flow of participants, therapists, centres through the study

After 108 patients were screened for eligibility, 105 were enrolled in the study, giving a participation rate of 97%. Among the 105 participants who enrolled, 63 were recruited at Rouen University Hospital and 42 at Jacques Monod Hospital. The therapists at these centres had worked in pulmonary rehabilitation for at least 5 years. One participant withdrew consent and a further two were lost to follow-up for reasons deemed to be unrelated to the intervention, giving a follow-up rate of 97% (Figure 3).

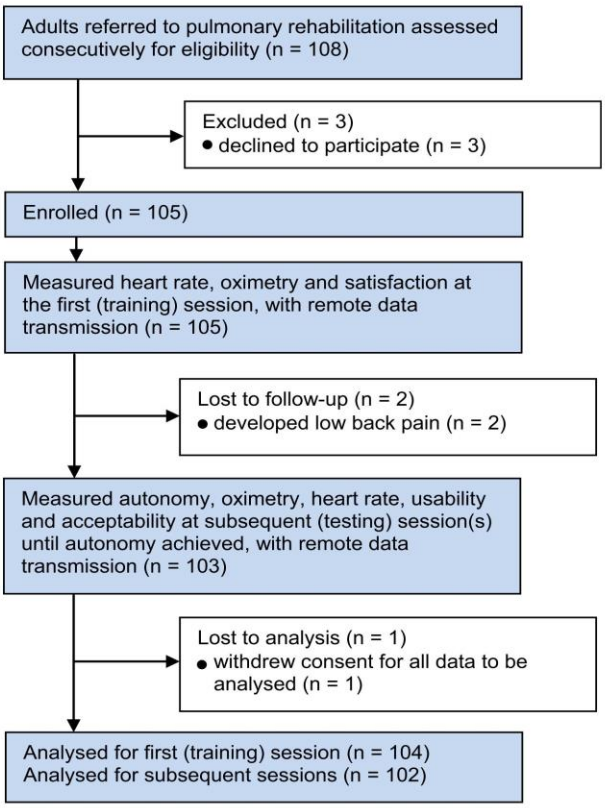

Figure 3. Flow of participants through the study.

Compliance with the study protocol

The prospective study registration occurred in two parts: one indicating the methods involving the entire study cohort and the other indicating the methods involving the subgroup of five participants. All registered outcome measures from both registered protocols were presented. Apart from the loss to follow-up outlined above, there were no departures from the planned study methods.

Characteristics of participants

The participants' characteristics are summarised in Table 1. Briefly, 36% were women, 84% had COPD as primary diagnosis and 19% were long-term oxygen users. Most commonly, they had a severe obstructive respiratory disease with thoracic distension. Individual participant data of the five participants involved in the technical validation of the device, all of whom had COPD, are shown in Table 2.

Ability to record and transmit oximetry data autonomously

Most participants became autonomous quickly: 88 at the first testing session (86%, 95% CI 78 to 92), a further 11 at the second testing session (cumulatively 97%, 95% CI 91 to 99), and the remaining three at the third testing session (cumulatively 100%, 95% CI 96 to 100). The session-by-session and cumulative data are presented in Figure 4. Participants who were not autonomous at activating the data transmission system at the first testing session were significantly older and had lower exercise capacity, as shown in Table 3. However, they also had a significantly longer delay between their teaching session and their first testing session (Table 3).

Table 1
Characteristics of the participants.

Characteristic	Participants (n = 104)
Gender, n female (%)	37 (36)
Age *(yr)*, median (IQR)	64 (57 to 70)
Height *(cm)*, mean (SD)	168 (9)
Body mass *(kg)*, mean (SD)	72 (21)
Body mass index *(kg/m^2)*, median (IQR)	24.2 (21.5 to 28.2)
Primary diagnosis, n (%)	
COPD	87 (84)
GOLD I	6 (7)[a]
GOLD II	20 (23)[a]
GOLD III	30 (34)[a]
GOLD IV	31 (36)[a]
asthma	4 (4)
restrictive lung disorder	8 (8)
other	5 (5)
FEV_1 *(l)*, median (IQR)	1.2 (0.8 to 1.8)
FEV_1 *(%)*, median (IQR)	43 (33 to 68)
FVC *(l)*, median (IQR)	2.5 (2.1 to 3.5)
FEV_1/FVC *(%)*, median (IQR)	53 (38 to 64)
Vital capacity *(l)*, mean (SD)	2.9 (0.9)
Residual volume *(l)*, median (IQR)	3.4 (2.3 to 4.5)
Total lung capacity *(l)*, mean (SD)	6.3 (1.7)
Inspiratory capacity *(l)*, mean (SD)	1.9 (0.7)
VO_{2peak} *(ml/kg/min)*, median (IQR)	14 (12 to 17)
W_{peak} *(W)*, median (IQR)	70 (50 to 90)
6MWT distance *(m)*, mean (SD)	433 (119)
Long-term oxygen use, n (%)	20 (19)

Percentages may not sum to 100 due to the effects of rounding.
COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GOLD = stage of severity according to the Global Initiative for Lung Disease, VO_{2peak} = maximal oxygen consumption, W_{peak} = maximal workload achieved during cardiopulmonary exercise testing, 6MWT = 6-minute walk test.
[a] GOLD percentages are calculated within the 87 participants with COPD.

Table 2
Individual participant data and summary data for the subgroup (n = 5) involved in the assessment of the validity of the transmitted data.

ID	Age (yr)	Body mass (kg)	Height (cm)	BMI (kg/m^2)	FEV_1 (l)	FEV_1 (%)	FVC (l)	FVC (%)	FEV_1/FCV (%)	6MWT (m)	VO_{2peak} (ml/kg/min)	W_{peak} (W)
1	52	114	179	35.6	1.5	39	4.0	86	37	583	16	110
2	47	60	161	23.1	0.7	25	2.1	68	32	435	11	40
3	62	54	154	22.8	0.7	36	2.1	88	34	451	NA	70
4	67	66	162	25.1	1.2	47	2.2	68	54	450	12	60
5	64	44	151	19.3	0.7	40	2.0	90	36	NA	15	40
Median (IQR)	62 (50 to 66)	60 (49 to 90)	161 (153 to 171)	23.1 (21 to 30)	0.7 (0.7 to 1.3)	39 (31 to 44)	2.1 (2.0 to 3.1)	86 (68 to 89)	36 (33 to 45)	451 (439 to 550)	14 (11 to 15)	60 (40 to 90)

BMI = body mass index, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, NA = not assessed, VO_{2peak} = oxygen consumption at the peak of exercise, W_{peak} = workload at the peak of exercise, 6MWT = 6-minute walk test.

Satisfaction with the transmission system

After the initial teaching session, 100% (95% CI 96 to 100) of the participants agreed or strongly agreed that the equipment was easy to use and 98% (95% CI 93 to 100) agreed or strongly agreed that they would be willing to carry out their entire pulmonary rehabilitation program with this equipment. Overall, 100% (95% CI 96 to 100) of the participants were satisfied or very satisfied with the equipment (Figure 5). The data used to generate this figure are presented numerically in Table 4 (on the eAddenda).

These proportions were similar at the session where autonomy was reached, although two further improvements were noted. A greater proportion of participants strongly agreed that they would carry out their entire pulmonary rehabilitation program with the equipment, and a greater proportion stated that they were very satisfied with the equipment (both $p < 0.01$) (Figure 5).

Validity of the transmitted data

Percentage of usable data

In total, 238 sessions were performed: 104 teaching sessions, 102 baseline testing sessions, 14 repeat testing sessions required to reach autonomy (including two sessions for one participant in the subgroup), and 18 further sessions for the subgroup (ie, five participants who performed four additional sessions after their baseline testing session minus two sessions already included in the repeat testing session required to reach autonomy). Among these, 234 sessions were successfully retrieved from the transmission device[b] server, which equated to 98% of sessions having usable data (95% CI 96 to 100). Data were typically available a few minutes after removal of the pulse oximeter. In some rare cases (related to GSM network disturbance), the information was stored in the transmission device and transmitted as soon as the network worked properly. If the information was not transmitted within a day, it was never transmitted; this accounted for the 2% of sessions having unusable data.

From the subgroup of five participants who performed five sessions, all 25 of these sessions were successfully retrieved and used to assess the validity of the data. The mean duration of these transmissions was 49 minutes (SD 1). Artefacts identified in either Database 1 or Database 2 were filtered from both sets of data, which resulted in a mean of 99.1% of usable paired data (SD 0.6) within these 25 sessions. This generated over 65 000 pairs of data points for comparison between the local oximeter and the remote database.

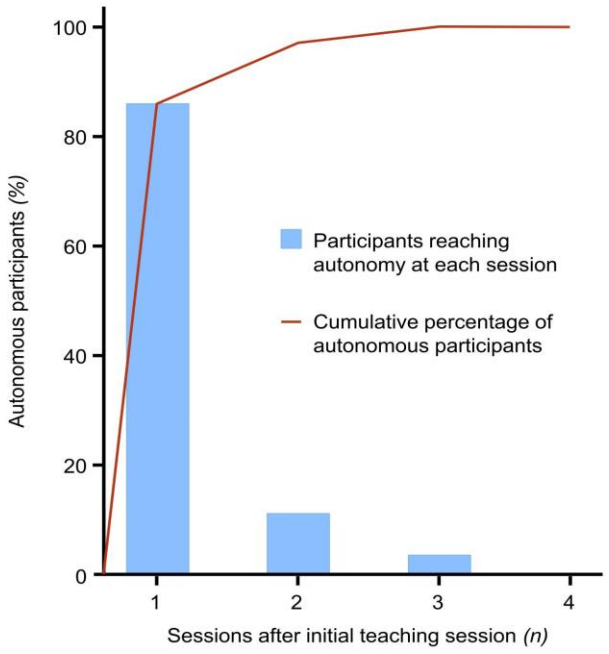

Figure 4. Number of sessions needed for participants to become autonomous with the data transmission device.

Mean absolute difference and Bland-Altman limits of agreement

The mean absolute difference and the limits of agreement between the data stored locally in the oximeter memory (Database 1) and the transmitted data (Database 2) are presented in Table 5. Corresponding Bland-Altman plots are presented for HR and for SpO_2 in Figure 6 and Figure 7. (For individual participant data see Table 6 on the eAddenda and for the statistical analysis file, see Appendix 1 on the eAddenda.)

Percentage agreement

The HR data had a mean percentage exact agreement of 72% (SD 9) and a mean percentage similar agreement of 99% (SD 1). The SpO_2 data had a mean percentage exact agreement of 87% (SD 3) and a mean percentage similar agreement of 100% (SD 0).

Table 3
Group characteristics of participants who were or were not autonomous at activating the data transmission monitoring system at the first testing session.

Characteristic	Participants		Between-group comparison[a]
	Autonomous at first testing session (n = 88)	Not autonomous at first testing session (n = 14)	p
Gender, n female (%)	30 (34)	6 (43)	0.56
Age (yr), median (IQR)	62 (55 to 69)	69 (63 to 75)	0.03
COPD diagnosis, n (%)	74 (84)	12 (86)	1.00
W_{peak} (W), median (IQR)	70 (50 to 90)	40 (31 to 60)	0.02
W_{peak} (%), median (IQR)	60 (44 to 68)	40 (35 to 52)	0.05
Time between teaching session and first testing session (d), median (IQR)	3 (2 to 6)	7 (3 to 20)	0.02

COPD = chronic obstructive pulmonary disease, W_{peak} = workload at the peak of exercise.

[a] Chi-squared test for age and diagnosis and Mann-Whitney test for other characteristics.

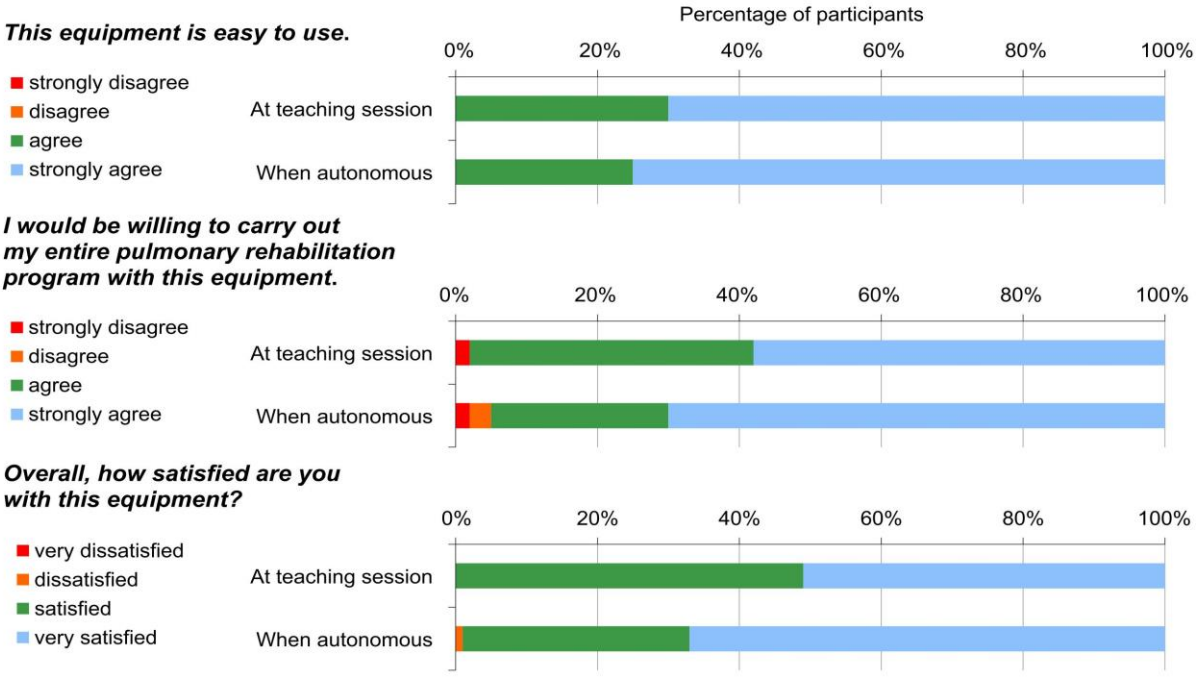

Figure 5. Participants' satisfaction with the data transmission equipment at the initial teaching session and when autonomy with using the equipment was first demonstrated.

Discussion

The main findings of this study were that participants considered the telemonitoring system to be user-friendly, they quickly learnt to use it to transmit their oximetry data autonomously, and the transmitted data were valid. These findings were generated using data from people with chronic lung disease referred to pulmonary rehabilitation, and there was minimal loss to follow-up during the study. The initial teaching session reflected that usually carried out in telerehabilitation programs.[25] The data collection process closely mimicked the conditions under which such people would use the system to collect and transmit the oximetry data autonomously. The results therefore indicate that the system is suitable for use in telerehabilitation and that the data can be interpreted as clinically equivalent to the acquired signal.

Any data transmission system will only be helpful for telemonitoring if patients can use it autonomously, so it is reassuring that the study participants readily learnt to use the system with minimal training. The user-friendliness of the system was evident in the rapid achievement of autonomy (86% of participants at the first testing session, rising to 97% at the second session and 100% at the third session). This could be considered a conservative estimate because participants were only taught once, whereas in clinical practice, patients with concerns might be offered repeat training or other support (eg, written materials). Routine provision of a well-written instruction leaflet might produce even more rapid attainment of autonomy, which would allow clinicians to anticipate autonomy after the teaching session for almost every patient.

Participants who were not autonomous at the first testing session were significantly older. Although these results should be interpreted with caution, they might be explained by older subjects being less familiar with using new technology. Furthermore, as both ageing and COPD are associated with increased prevalence of cognitive dysfunction, executive function impairment may have altered learning processes in older patients.[36,37] This notion is strengthened by the fact that about 10% of the patients with COPD referred to pulmonary rehabilitation have cognitive dysfunction,[38] which is a similar percentage to the 14% of participants who were not autonomous at the first testing session in the present study. Older patients might therefore be a suitable target group for the additional training or support materials. However, lack of autonomy at the first testing session was also strongly associated with a longer time between teaching and testing. Therefore, clinicians could try to schedule training as close as possible to when patients will commence telerehabilitation.

When study participants were questioned about the system, 100% found it easy to use, 98% agreed to use it for their whole pulmonary rehabilitation program, and 100% were satisfied with the system. Moreover, a proportion of participants changed from expressing agreement to strong agreement with those sentiments when they achieved autonomy (Figure 5). These favourable results have good external validity because this study is very likely to have had a representative sample of pulmonary rehabilitation participants due to the consecutive sampling, high uptake rate and low dropout rate.

The analyses of the validity of the transmitted data were also reassuring. There was an excellent proportion of usable data, with a very low rate of artefacts (0.9%). Most of the time, these artefacts were due to the oximeter (probably resulting from movement at the finger probe – a well-known problem with oximetry during exercise), and were transmitted through the transmission device[b]. The transmission process itself generated very few artefacts. As a consequence, remote measurements were valid compared to locally stored data. The data that were transmitted through the remote system showed very little discrepancy against the locally stored data. The mean absolute difference of 0.365 beats/minute for HR was well below the pre-nominated threshold of acceptable error (3 beats/minute). Similarly, the mean absolute difference of 0.133 % for SpO_2 was well below the pre-nominated threshold of acceptable error (3%). Similarly, the limits of agreement for both HR and SpO_2 were smaller than their respective pre-nominated threshold. Concerning the analyses of agreement, the percentage exact agreement was high at 72% for HR

Table 5
Mean absolute difference (SD) and limits of agreement between data stored locally in the oximeter memory (Database 1) and the transmitted data (Database 2).

Measure	Mean absolute difference (SD)	Limits of agreement	
		Lower bound	Upper bound
HR *(beats/minute)*	0.365 (0.136)	−0.844	1.044
SpO_2 *(%)*	0.133 (0.034)	−0.297	0.337

HR = heart rate, SpO_2 = transcutaneous oxygen saturation.

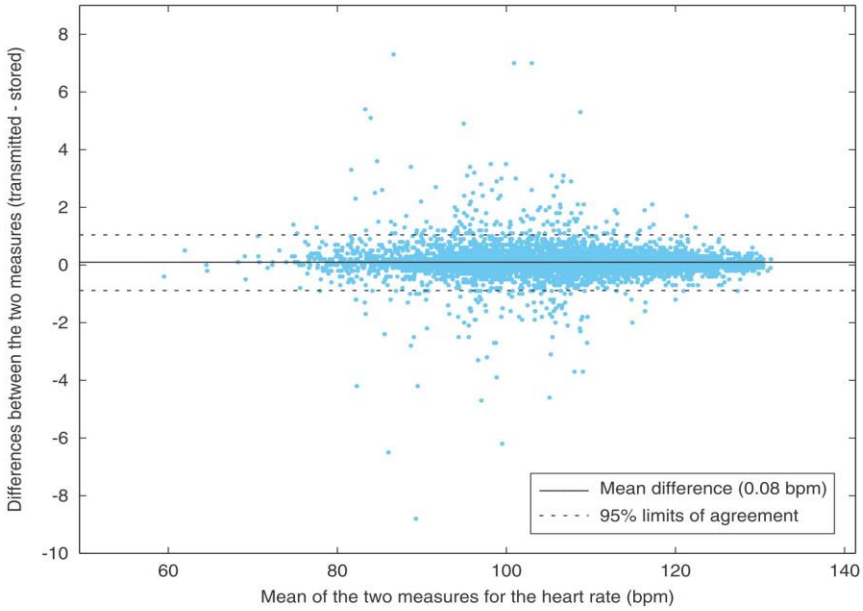

Figure 6. Bland-Altman plots for heart rate (HR) in beats per minute (bpm). The point-to-point difference between the two databases (transmitted minus stored) is plotted against the mean of the two measures. 95% limits of agreement (lower and upper bounds) were −0.844 and 1.044.

and 87% for SpO_2. However, percentage similar agreement was proposed as being sufficient for clinical practice, and these values were excellent at 99% for HR and 100% for SpO_2. In other words, the transmission device is responsible for a clinically important error in < 1% of the data for each of the variables considered. Together, these analyses indicate that the transmission system was suitable for telemonitoring purposes.

The reliability of data acquired through a telemonitoring system has previously been studied in healthy participants. Tang et al appraised the validity of the eHAB videoconference telerehabilitation system configured to receive data from a similar pulse oximeter[d 30]. Although the mean absolute difference found in their study for HR and SpO_2 (0.21 beats/minute and 0.04%, respectively) were comparable to the present study, the exact agreement between data from the local and remote devices differed. Around 9% of data were omitted and 11% duplicated in their study versus <1% of artefacts in the present study. This might be due to differences between the systems. Alternatively, artefacts may be higher with healthy participants because they are less familiar with wearing oximeters than people with COPD taking part in pulmonary rehabilitation, leading to more unwanted movement or pressure around the probe. In the study by Tang et al,[30] difficulties with the local network led the authors to suggest the use of a mobile telephone network, which is what we did in the present study. Because the two centres involved in this study were in the same country, further testing of the system in the mobile networks of other countries should be performed.

The favourable results in this study reinforce some preliminary studies, which suggested that telerehabilitation is acceptable,[19]

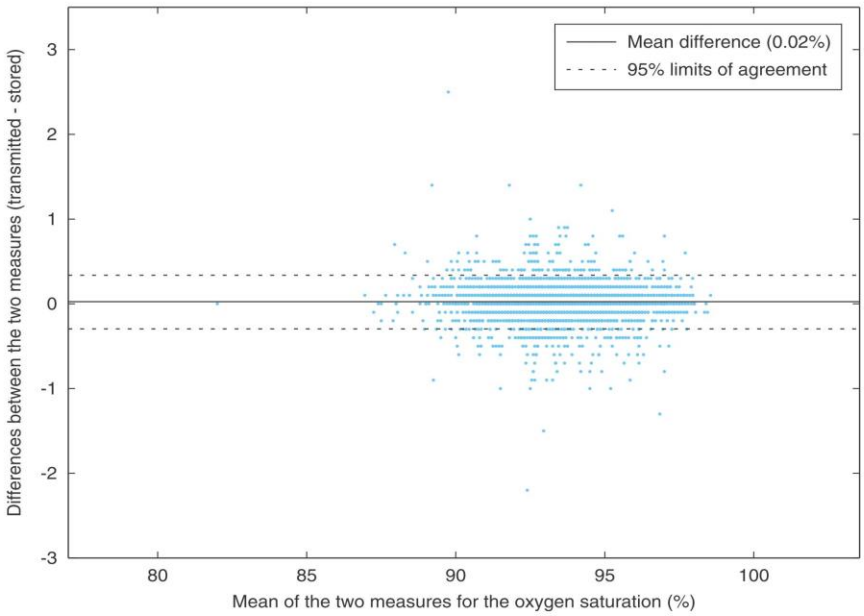

Figure 7. Bland-Altman plots for oxygen saturation (SpO_2). The point-to-point difference between the two databases (transmitted minus stored) is plotted against the mean of the two measures. 95% limits of agreement (lower and upper bounds) were −0.297 and 0.337.

feasible and safe.[21,24,25] However, the data produced by different systems can differ greatly in terms of the proportion of artefact and the magnitude of error in the remaining data. With an inaccurate telemonitoring system, exercise training may not be progressed appropriately or safety concerns may not be recognised and addressed. Thus, clinicians should either use a system that has been shown to produce satisfactory results (such as the one used in this study) or confirm that an alternative system is also satisfactory prior to its implementation. It is also important to remember that the decision to progress exercise would also depend on other factors such as breathlessness.

Telerehabilitation can vary in how directly patients are observed during their exercise. At one extreme, patients exercise at a scheduled time with real-time remote supervision. This is often done with videoconferencing of multiple patients in a virtual 'class', as has been described in detail elsewhere.[21,24,26,39] At the other extreme, patients exercise without real-time supervision and their exercise data are transmitted to the hospital or medical centre at the end of a training session, as in the present study. Based on these data, clinical staff advise the patient about progression of the exercise or address safety concerns before the next exercise session. Qualitative studies[40,41] of the factors that influence patients' attitude, adherence and satisfaction during telerehabilitation suggest that these two approaches may have different advantages and disadvantages. Real-time videoconferencing allows more immediate observation of exercise, which may reassure some patients.[40] An accurate oximetry monitoring system may foster this reassurance. Peer support is also facilitated by the videoconferencing approach.[39] Some patients may have privacy concerns with this approach.[42] In contrast, when exercise is without video supervision, other patients have reported feeling motivated and/or empowered by learning how to exercise at home and to use the new technology to monitor themselves.[40] An accurate oximetry monitoring system may reassure the clinician about the patient's response to the exercise training. This more independent approach also facilitates adherence by allowing training to be performed whenever it suits the patient.[41] Moreover, this system informs the therapist of the number and duration of sessions performed. It also provides an objective measurement of the duration of training performed compared to the prescribed duration. Franke et al[43] recently suggested that a telemonitoring system only based on the transmission of the time spent cycling could improve regular physical activity and quality of life in patients with COPD. Moreover, the addition of a phone call if required (eg, if the prescribed time was not reached) could further increase daily training time.[43] Thus, the telemonitoring system used in this study could help therapists to target patients who need to be contacted according to the amount of training (ie, frequency or duration) or the need to adapt it (eg, training intensity based on HR not reached[2] or safety issue).[44] Furthermore, it could be used in a hybrid approach, where the oximeter readings were turned to face the camera during supervised exercise, but the therapist still would have access to the transmitted HR and SpO_2 data from exercise sessions undertaken at other times.

Telerehabilitation is often discussed in relation to people living in rural and remote locations, but there are other populations that may benefit. These include: patients without transport to local centre-based pulmonary rehabilitation programs, patients living near hospitals that do not have staff skilled in pulmonary rehabilitation, and patients who cannot leave home due to carer duties.

This study had some strengths and limitations. A large cohort of participants was used to assess feasibility and acceptability of a telerehabilitation intervention. Moreover, this was a multicentre study enrolling every patient referred for pulmonary rehabilitation without disease restriction, thereby providing important external validity to the results. The external validity of the study is further reinforced by the similar characteristics of the participants and of cohorts undertaking pulmonary (tele)rehabilitation in Australia,[17,29] Canada,[23] Italy,[24,38] Greece,[28] Denmark,[20] and the Netherlands.[18,25] The intervention was largely accepted, with a participation rate of 97%. Limitations of the present study included the small sample size of the subgroup of participants in the assessment of the validity of the transmitted data. However, the recordings from five patients during five 45-minute cycling sessions with a sample frequency of 1 Hz enabled the analysis of more than 65 000 paired data points for HR and SpO_2. We are therefore confident in the interpretation of the results for these outcomes. Second, cognitive function, which is known to be frequently altered in patients with COPD,[45–47] and educational level were not evaluated. Each could have influenced the usability of the system. Further study could specifically assess the feasibility of telehealthcare in people with cognitive impairment. Third, patient satisfaction with telehealth technology was assessed with a non-validated Likert scale.[23] Finally, electrocardiography is the gold standard to assess HR and the use of pulse oximetry might have introduced some bias. However, telerehabilitation programs typically use pulse oximetry to monitor both HR and SpO_2, rather than ECG.[27] This is likely related to the fact that pulse oximetry is much simpler to use by the patient in the home environment and, moreover, it provides all the necessary information. Therefore, the results are more clinically relevant.

In conclusion, the telemonitoring system used in this study is sufficiently accurate and valid for use in home-based pulmonary rehabilitation for patients with chronic respiratory disease. It is reasonable to consider that the transmitted data are clinically equivalent to the acquired signal and could therefore be used for telerehabilitation. The system was user-friendly and almost every participant used it autonomously after the first teaching session. Moreover, they were agreeable to using it for their entire pulmonary rehabilitation and were satisfied with the system.

What was already known on this topic: People with chronic lung disease benefit from exercise-based pulmonary rehabilitation, via reduced dyspnoea, improved exercise capacity, and better quality of life. Delivering pulmonary rehabilitation in the patient's home is effective and may help to reach the large number of people with chronic lung disease.

What this study adds: Most people referred to pulmonary rehabilitation can quickly learn to operate equipment used for remote monitoring of oximetry during home exercise. These patients consider remote monitoring of oximetry acceptable. Oximetry recordings can be transmitted with minimal artefact or invalid data.

Footnotes: [a] Nonin 3150, Nonin Medical Inc., Plymouth, USA. [b] Twitoo®, H2AD, Saint-Étienne, France. [c] H2AD, Saint-Étienne, France. [d] Nonin 9560, Nonin Medical Inc., Plymouth, USA.

eAddenda: Tables 4 and 6, Figure 2 and Appendix 1 can be found online at DOI: https://doi.org/10.1016/j.jphys.2018.11.002.

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Competing interest: The authors state that they have no conflicts of interest.

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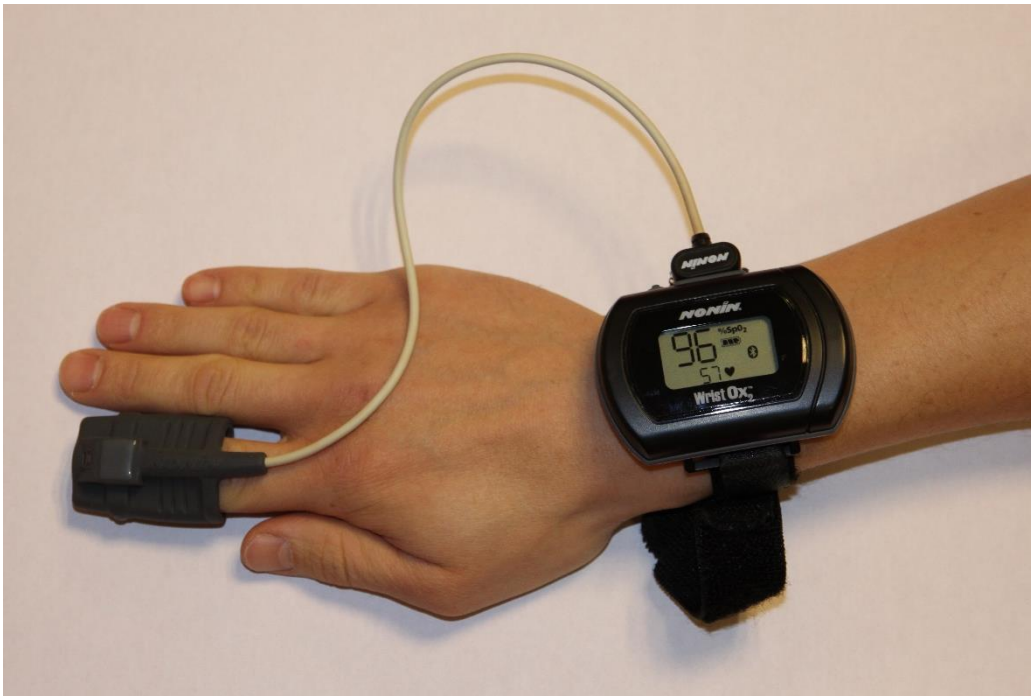

Figure 2. Oximeter used for the home telemonitoring. The oximeter is connected to the telemonitoring system for data transmission through a Bluetooth network. Data are subsequently transmitted to the telemonitoring platform through the Global System for Mobile communications.

Table 4
Participants' satisfaction with the data transmission equipment at the initial teaching session and when autonomy with using the equipment was first demonstrated.

Satisfaction with the telemonitoring system	Agreement	Time point	
		Initial teaching session (n = 104)	Session where autonomy with using the equipment was demonstrated (n = 102)
This equipment is easy to use, n (%)	Strongly agree	73 (70)	77 (75)
	Agree	31 (30)	25 (25)
	Disagree	0 (0)	0 (0)
	Strongly disagree	0 (0)	0 (0)
I would be willing to carry out my entire pulmonary rehabilitation program with this equipment, n (%)	Strongly agree	60 (58)	71 (70)
	Agree	42 (40)	26 (25)
	Disagree	0 (0)	3 (3)
	Strongly disagree	2 (2)	2 (2)
Overall, how satisfied are you with this equipment?, n (%)	Very satisfied	53 (51)	68 (67)
	Satisfied	51 (49)	33 (32)
	Dissatisfied	0 (0)	1 (1)
	Strongly dissatisfied	0 (0)	0 (0)

[a] Data are summarised as count (%). Percentages may not sum to 100 due to the effects of rounding.

I.5. Lever les freins à l'accès de la réhabilitation respiratoire à domicile : fonction cognitive et réhabilitation respiratoire

Le modèle proposé pour faire face au manque de structures d'évaluation et de réhabilitation consiste donc à délocaliser l'évaluation du patient et le déroulement de la réhabilitation elle-même hors des centres spécialisés, incluant le domicile. Par ailleurs, l'objectif de la réhabilitation respiratoire n'est pas seulement l'amélioration de la capacité physique, de la dyspnée et de la qualité de vie (40) mais également de favoriser un changement de comportement, incluant le maintien d'une activité physique autonome sur le long terme afin de conserver les bénéfices acquis au cours du programme initial (37, 51).

Dans ce contexte, le changement de comportement nécessaire pour initier ou maintenir un programme d'exercice à domicile ainsi que la capacité à utiliser des technologies de santé (dans le cadre du telemonitoring au cours d'un programme de réhabilitation réalisé à domicile par exemple) nécessitent tous deux l'implication des fonctions cognitives. On sait que la dysfonction cognitive est une des conséquences « systémiques » de la BPCO (90-94). Sa prévalence est plus importante que chez les sujets non BPCO de même âge et varie selon les études (de 36 à 57%) (90-94). Elle pourrait atteindre 88% chez les patients hypoxiques (16).

Les fonctions cognitives font référence à l'ensemble du processus neuronal d'ordre supérieur qui sous-tend la gestion de l'information par laquelle un comportement peut être adapté (16, 95). Les fonctions cognitives peuvent être divisées en plusieurs domaines cognitifs :

- Traitement de l'information ;
- Attention et concentration ;
- Mémoire ;
- Fonctions exécutives ;

- Auto contrôle (16).

Les mécanismes physiopathologiques responsables de la dysfonction cognitive chez les patients atteints de BPCO ne sont pas encore compris mais incluent probablement l'hypoxémie chronique, l'hypercapnie, l'altération de la fonction respiratoire, l'inflammation systémique, l'inactivité, le tabagisme, le remodelage cérébral ainsi que les exacerbations répétées (16, 95, 96).

La dysfonction cognitive est associée à une moins bonne qualité de vie (97) ainsi qu'à un taux plus important d'hospitalisations (98) et de mortalité (16, 95, 98, 99). De plus, elle est associée à des comportements de santé non adaptés tel qu'une faible compliance avec les traitements inhalés (100) ou encore des difficultés de réalisation et d'obtention d'un sevrage tabagique (101).

Malgré son importance pour adopter un changement de comportement positif vis à vis de l'activité physique, il existe peu de données concernant la prévalence de la dysfonction cognitive parmi les patients adressés en réhabilitation respiratoire (102, 103) ni sur la façon dont elle peut en affecter les bénéfices (104). Par ailleurs, bien que certaines études aient suggérées un bénéfice potentiel de la réhabilitation respiratoire sur les fonctions cognitives (105, 106), il existe peu de données sur le maintien de ces bénéfices à distance de la réhabilitation ainsi que l'impact des fonctions cognitives sur le maintien d'une activité physique après le programme initial (107). Enfin, comme la réhabilitation respiratoire peut être proposée à domicile via l'utilisation de technologies de santé, l'impact des fonctions cognitive sur la possibilité d'utiliser de tels dispositifs nécessite d'être évalué.

Étude n°5

Prévalence de la dysfonction cognitive parmi les patients atteints de BPCO adressés pour réhabilitation respiratoire, et effets à moyen terme de la réhabilitation respiratoire sur les fonctions cognitives

Mid-term effects of pulmonary rehabilitation on cognitive functions in people with severe chronic obstructive pulmonary disease.

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ORIGINAL RESEARCH

Mid-Term Effects of Pulmonary Rehabilitation on Cognitive Function in People with Severe Chronic Obstructive Pulmonary Disease

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Purpose: Cognitive dysfunction is a common impairment associated with COPD. However, little is known about 1) its prevalence among those subjects referred for pulmonary rehabilitation (PR), 2) how it may affect the benefit of PR, 3) whether PR improves cognitive function and 4) whether cognitive dysfunction affects the usability of telehealth technology usually used to deliver in-home PR.

Patients and Methods: Fifty-six subjects with stable COPD (54% females, mean age 62 years (SD 9) and median FEV_1 0.9 L (IQR 0.7 to 1.1)) participated in this multicenter observational study and performed 24 sessions of PR. The Montreal Cognitive Assessment tool (MoCA) was used to assess the occurrence of mild cognitive dysfunction (using a screening cutoff <26) at baseline, completion of PR and 3 months of follow-up.

Results: Mild cognitive dysfunction was found in 41 subjects (73% [95% CI: 60 to 83%]). The MoCA score significantly improved following PR for those people with baseline mild cognitive dysfunction ($p<0.01$). There was no significant difference in clinical outcomes between those people with or without mild cognitive dysfunction following PR nor in the proportion of subjects who were autonomous in using the telemonitoring system (83% compared with 71%, $p=0.60$).

Conclusion: Mild cognitive dysfunction is highly prevalent among those people with COPD referred for PR but does not affect the benefits of PR nor the usability of a telemonitoring system. PR may improve short- and mid-term cognitive function for those people who experience mild cognitive dysfunction at the time they are referred to PR.

Keywords: COPD, pulmonary rehabilitation, exercise, cognitive dysfunction

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death worldwide[1] and its prevalence, as high as 10% in adults over 40 years old,[2] is planned to increase in the next decade.[3] This respiratory disease progressively leads to physical inactivity, muscle deconditioning and worsening dyspnea.[4] Pulmonary rehabilitation (PR), including exercise training and education, is therefore recommended for these patients.[5,6] The aim of PR is not only to improve exercise capacity, dyspnea and quality of life[7] but also to promote behavior changes in order to maintain long-term adherence to health-enhancing comportments, including exercise maintenance.[5] The behavior changes necessary to maintain an in-home exercise program are driven by the cognitive functions which refer to a high-order neural process that underpins information handling by which a behavior can be adapted.[8,9] However, cognitive dysfunction is another

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systemic feature impairment associated with COPD and may be as prevalent as 88% in hypoxic subjects.[9] Although the mechanisms have not been clearly elucidated yet, these may involve chronic hypoxemia, chronic hypercapnia, lung function impairment, systemic inflammation, inactivity, smoking, cerebral atrophy or structural changes and repeated acute exacerbations.[8–10]

Cognitive dysfunction in COPD is associated with worst outcome such as altered quality of life,[11] higher rate of hospitalization[12] or death,[8,9,12,13] as well as with unsuitable health behavior, such as poor intake of inhaled treatments[14] or difficulties in smoking cessation.[15] However, little is known about its prevalence among those subjects referred for PR[16,17] and how it may affect the benefit or PR.[18] Though some studies have shown a potential improvement in cognitive function with PR,[19,20] little is known about whether these benefits are subsequently maintained and whether they impact exercise maintenance following PR.[21] In addition, because of a limited access to PR (mainly located in urban areas) and a number of barriers to attend or participate in,[22–24] PR is often delivered in the home environment with the use of telehealth technologies.[25] However, the impact of cognitive function on the usability of telehealth technology usually used to deliver in-home PR has not been studied yet. Therefore, we hypothesized that cognitive dysfunction is highly prevalent among those people with COPD referred for PR but has the potential to improve following PR. Additionally, we hypothesized that cognitive dysfunction may impede with the positive effect of PR as well as with the usability of telehealth technology and exercise maintenance following PR.

The primary aims of this study were to assess the prevalence of cognitive dysfunction among people with COPD referred for PR and the mid-term effects of PR on cognitive function (3 months after completion). Secondary objectives were to assess how cognitive dysfunction may affect the benefit of PR, telehealth technology usability and exercise maintenance following PR.

Methods

Study Design and Participants

This prospective multicenter observational study was approved by the French Ethics Committee Ile de France 1 (2017-juin-14586 ND), was prospectively registered at https://www.clinicaltrials.gov (NCT03244137) and conducted in accordance with the Declaration of Helsinki.

Subjects with a clinical diagnosis of COPD referred for PR at ADIR Association, Rouen University Hospital, France and Jacques Monod Hospital, Le Havre, France, were screened for eligibility between August 2017 and June 2019. They had to be 18 years and over, have a forced expiratory volume in 1 s (FEV1) <50% and be eligible to PR (ie, exertional or rest dyspnea and no medical contraindication to exercise). Subjects were not included if they were hospitalized for an acute exacerbation within the previous 3 months,[11,26] had an active alcoholism or had a history of psychiatric or neurovascular disease, cranial trauma, or other known disease associated with cognitive dysfunction. Other non-inclusion criteria included pregnancy or likely to be and guardianship. Subjects were excluded if the PR program was interrupted for more than 14 days due to severe acute exacerbation of COPD,[11,26] if they disrupted training before 18 sessions or performed less than 18 sessions in 4 months (non-adherent subjects). Written informed consent was obtained from all patients.

Clinical and Functional Assessment

Before attending the PR program and prior to participating in the study, every subject underwent an evaluation including pulmonary function tests[27] and cardiopulmonary exercise testing (CPET).[28]

Pulmonary Rehabilitation Program

Every subject participated in a 3 times per week for 8 weeks comprehensive outpatient PR program including respiratory physiotherapy, muscle strengthening, endurance training, self-management and nutritional support as necessary.

Peripheral muscle strengthening (3 sets of 12 movements at 70% of the one repetition maximum or using resistive bands) mainly focused on the lower limbs. Endurance training was progressive (from 15 to 45 mins, including a 5 mins warm-up and a 5 mins cool down periods) and the intensity was adjusted at the anaerobic threshold (manually derived from the initial CPET as the average of 4 methods: first break the minute ventilation curve, rise in the minute ventilation to oxygen consumption ratio without modification of the minute ventilation to carbon dioxide production ratio, rise in the end-tidal expired carbon dioxide gas and the Beaver's method[28,29]). Subsequently, the intensity was increased based on perceived exertion (dyspnea or muscular fatigue assessed using the Borg scale[30] as previously described[31]).

The self-management program was also individualized and constructed according to the « Living Well with COPD » program,[32] as well as with the French « Haute Autorité de Santé » guidelines for COPD self-management.[33] It covered the following topics: COPD knowledge, smoking cessation, management of acute exacerbations, inhaled treatments, physical activities, breathing management, healthy lifestyle, oxygen therapy, noninvasive ventilation, hobbies and traveling.

Usability of a Telemonitoring System

The first subjects were also invited to participate in a second prospective observational study aiming to assess whether subjects referred to pulmonary rehabilitation could easily learn to use a system for remote transmission of oximetry data. This second study, offered to every subject with chronic lung disease referred to pulmonary rehabilitation (without any other restriction) took place within the same period in both centres but ended earlier.[34]

Briefly, an investigator physiotherapist taught the participants how to use the telemonitoring system and subsequent sessions were scheduled to determine when the subjects became autonomous with transmitting their data via the telemonitoring system.[34]

Outcomes

Outcomes were assessed before PR, at the end of PR and 3 months following the completion of PR.

The primary outcome was cognitive function assessed with the Montreal Cognitive Assessment tool (MoCA).[17,35,36] Three versions of the tool are currently available to avoid any learning effects and were used in a cross-over randomized order throughout the evaluations (computer-generated sequence and concealed allocation). The same investigator performed the three evaluations for a given patient. A screening cutoff <26 was used to assess the occurrence of mild cognitive dysfunction.[17,36]

Secondary outcomes were health-related quality of life using the Saint George's Respiratory Questionnaire total score and sub-scores,[37] anxiety and depression using the Hospital Anxiety and Depression scale[38] and functional capacity (only assessed before and at the end of PR) using the six-minute walk test[39] and the six-minute stepper test.[40–42] In addition, autonomy in using the telemonitoring system was granted if the procedure was repeated successfully at the first session after initiation.

Statistical Analysis

The normality of the data was assessed using the Kolmogorov–Smirnov test. Categorical data were expressed as counts (% and 95% confidence interval (CI)) and continuous data were expressed as mean (SD) or median (25th–75th percentile) according to the distribution. Comparison of outcomes between baseline, following PR and 3 months following PR was performed using either repeated ANOVA (and Tukey post hoc tests) or a Friedman test (and a Wilcoxon test as a post hoc test for pairwise comparisons) according to the distribution. The change in the proportion of subjects with a MOCA score <26 was assessed using the Cochran test.

To assess the effects of cognitive dysfunction on the benefit of PR, exercise maintenance following PR and telehealth technology usability, subjects were separated into two groups according to their baseline score on the MOCA tool (<26 or ≥26). Difference in outcomes between groups was assessed using either an independent Student's *t*-test or a Mann–Whitney test for quantitative data and a Fisher exact test for categorical data. A p-value <0.05 was considered as statistically significant. SPPS software version 25 was used for all analyses.

Results

Subjects

Two hundred nine subjects were screened for eligibility and 56 were included in the study (Figure 1). Fifty-four percent of the participants were women, their mean age was 62 (SD 9) years, their median FEV1 was 0.9 L (IQR 0.7 to 1.1) and their aerobic capacity was decreased (mean VO2: 12 (SD 3) mL/kg/min). Among them, 19 also participated in the assessment of the usability of a telemonitoring system. Mild cognitive dysfunction was found in 41 subjects (73% [95% CI: 60% to 83%]). Their baseline characteristics were not significantly different from those people without cognitive dysfunction but they had the worst quality of life and a lower educational level (Table 1). Thirty-seven subjects were assessed following PR and 22 subjects 3 months thereafter (see Figure 1 for reasons of drop-out). Comparisons between subjects who did complete PR and those who did not, and between subjects that attended the 3 months follow-up and those who did not are shown in Table S1 and Table S2, respectively. The same comparisons for those subjects with a baseline MoCA <26 are shown in Table S3 and Table S4, respectively.

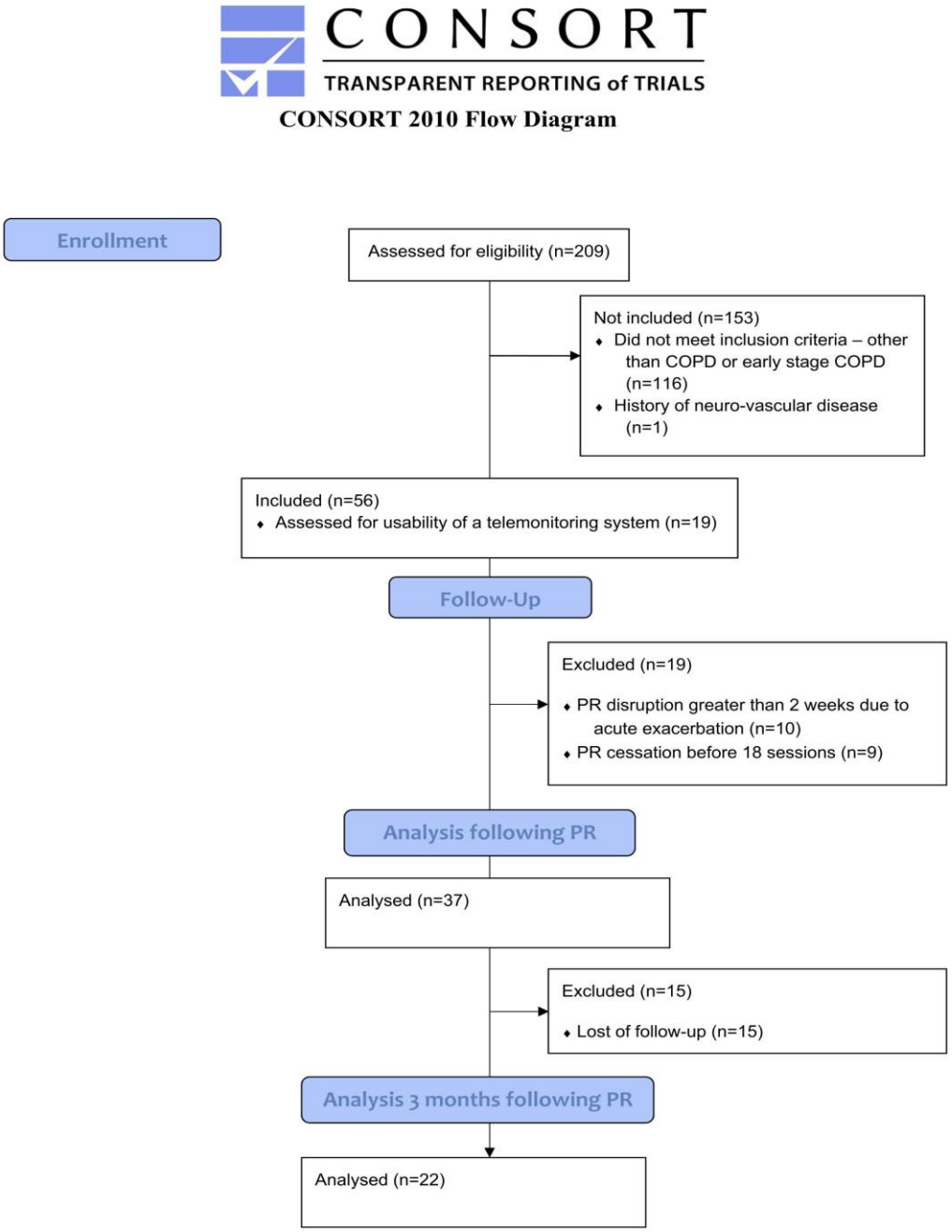

Figure 1 Study flow diagram.

Primary Outcome

The MoCA score significantly increased during the follow-up period ($p<0.01$), mainly due to a significant increase in the median score between baseline and 3 months following PR (from 22 (IQR 20 to 26) to 25 (IQR 23 to 28) respectively, $p<0.01$). The median MoCA score remained unchanged among those people without baseline mild cognitive dysfunction ($p=0.37$) while it significantly increased among those people with baseline mild cognitive dysfunction ($p<0.01$) mainly due to a significant improvement at the end of PR (from 21 (IQR 20 to 24) to 22 (IQR 20 to 26), $p<0.01$) which was sustained 3 months thereafter (median score: 24 (IQR 21 to 26), $p<0.01$) (Figure 2A).

Among the cognitive domains, only the median memory score significantly increased from baseline to post PR (from 3 (IQR 2 to 4) to 3 (IQR 3 to 5), $p=0.04$) and 3 months thereafter (4 (IQR 3 to 5), $p<0.01$). It was

Table 1 Demographic Characteristics of the Patients

Characteristics	Patients			Between-Group Comparison
	Total (n = 56)	MoCA <26 (n = 41)	MoCA ≥26 (n = 15)	*p*
Gender, n female (%)	30 (54)	20 (49)	10 (67)	0.37
Age (yr), mean (SD)	62 (9)	64 (9)	59 (11)	0.13
Body mass index (kg/m^2), mean (SD)	24.5 (5.2)	25 (5.5)	23.3 (4.2)	0.29
FEV_1 (L), median (IQR)	0.9 (0.7 to 1.1)	0.9 (0.6 to 1.2)	1.0 (0.7 to 1.1)	0.62
FEV_1 (%), median (IQR)	36 (28 to 44)	36 (28 to 44)	39 (32 to 44)	0.56
FVC (L), median (IQR)	2.3 (1.7 to 2.7)	2.2 (1.6 to 2.7)	2.3 (2.1 to 3.6)	0.36
FEV_1/FVC (%), mean (SD)	41 (10)	41 (10)	40 (9)	0.85
Residual volume (L), mean (SD)	4.1 (1.3)	4.2 (1.3)	3.8 (1.2)	0.35
TLC (L), mean (SD)	6.6 (1.4)	6.7 (1.4)	6.4 (1.5)	0.52
VO_{2peak} (mL/kg/min), mean (SD)	12 (3)	12 (3)	14 (3)	0.06
W_{peak} (W), median (IQR)	50 (39 to 63)	45 (36 to 60)	55 (39 to 73)	0.17
6MST (steps), median (IQR)	179 (113 to 209)	148 (103 to 202)	191 (156 to 246)	0.08
6MWT (meters), mean (SD)	386 (115)	377 (117)	409 (112)	0.39
BODE index, mean (SD)	5 (2)	5 (2)	4 (1)	0.09
Long-term oxygen, n (%)	27 (48)	22 (54)	5 (33)	0.23
Home non-invasive ventilation, n (%)	7 (13)	6 (15)	1 (7)	0.66
HAD-Anxiety, mean (SD)	10 (4)	10 (4)	9 (5)	0.42
HAD-Depression, median (SD)	8 (5 to 10)	8 (6 to 9)	6 (4 to 11)	0.50
Saint Georges Respiratory Questionnaire (%), mean (SD)	58 (16)	62 (15)	46 (15)	< 0.01
MoCA, median (IQR)	22 (20 to 26)	21 (20 to 24)	27 (26 to 28)	<0.01
Educational level[a]				0.01
Level I, n (%)	1 (2)	1 (2)	0 (0)	
Level II, n (%)	5 (9)	1 (2)	4 (27)	
Level III, n (%)	2 (4)	1 (2)	1 (7)	
Level IV, n (%)	8 (14)	4 (10)	4 (27)	
Level V, n (%)	17 (30)	14 (34)	3 (20)	
Level VI, n (%)	23 (41)	20 (49)	3 (20)	
Comorbidities				
Hypertension, n (%)	20 (36)	15 (37)	5 (33)	1.00
Hypercholesterolemia, n (%)	10 (18)	9 (22)	1 (7)	0.26
Diabetes, n (%)	4 (7)	1 (2)	3 (20)	0.06
Cardiopathies, n (%)	10 (18)	8 (20)	2 (13)	0.71
Surgery for NSCLC, n (%)	7 (13)	5 (12)	2 (13)	1.00
History of other cancer, n (%)	7 (13)	5 (12)	2 (13)	1.00

Notes: Fisher test for categorical data. Mann–Whitney or independent t-test for other characteristics. Percentages may not sum to 100 due to rounding. [a]Educational level was assessed according to the French National Institute of Statistics and Economic Studies Classification. Educational level ranged from I (Msc and higher) to V (interruption of the schooling during the first cycle of secondary education (before 16 years)).

Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; VO_{2peak}, maximal oxygen consumption; W_{peak}, maximal workload achieved during cardiopulmonary exercise testing; 6MST, six-minute stepper test; 6MWT, six-minute walk test; BODE, body-mass index; obstructive; dyspnea and exercise capacity index; HAD, anxiety and depression scale; MoCA, Montreal Cognitive Assessment tool; NSCLC, non-small-cell lung cancer.

further improved from post PR to 3 months following PR (p=0.04) (Figure 2B). There was no significant change in the proportion of people with mild cognitive dysfunction during the follow-up (p=0.20).

Secondary Outcomes

In the total population, PR significantly improved exercise capacity (6MST and 6MWT) and the SGRQ impact sub-score. The SGRQ impact sub-score was further improved

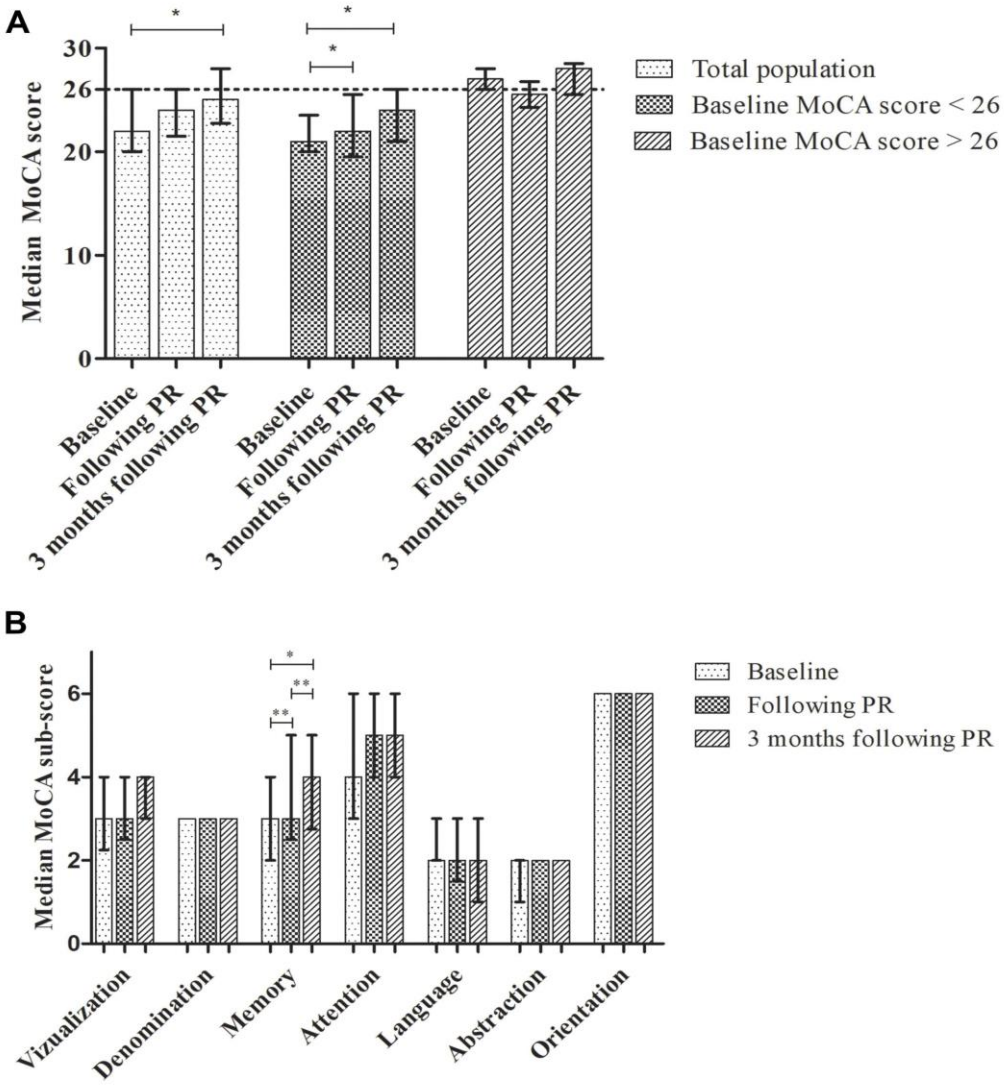

Figure 2 Evolution of the Montreal Cognitive Assessment tool total score (**A**) and sub-score (**B**). Data are shown as median (25th–75th percentile). Friedman test and Wilcoxon as a post hoc test for pairwise comparison for within-group comparison. Baseline: n=56; following PR: n=37, 3 months following PR: n=22. *p<0.01 **p=0.04.

3 months thereafter (p=0.02) (Table 2). There was no significant difference in outcomes between those people with or without mild cognitive dysfunction either following PR or at 3 months except for the median 6MST which was significantly higher for those people without mild cognitive dysfunction (218 (IQR 162 to 263) steps compared with 182 (IQR 121 to 310) steps, p=0.03) (Table 2).

The proportion of subjects who maintained a physical activity was not significantly different between those with or without mild cognitive dysfunction following PR (57% compared with 63%, respectively, p=1). The MoCA score 3 months following PR was not significantly different between those people who maintained a physical activity or not (24 (SD 3) and 25 (SD 3) respectively, p=0.71)

Finally, 10 out of 12 subjects (83%) with mild cognitive dysfunction were autonomous in using the telemonitoring system which was not significantly different from those subjects without mild cognitive dysfunction (5 out of 7 (71%), p=0.60).

Relationship Between the MoCA Score and Outcomes

At baseline, the MoCA score was negatively correlated with the SGRQ total score (r= −0.28, p=0.04; ie a higher score on the MoCA tool was associated with a better quality of life). The change in the MoCA score was not significantly associated with a change in any outcome following PR.

Table 2 Change in Secondary Outcomes Following and 3 Months After PR

Outcome	Timepoint			Within Group
	Baseline (n = 56)	**Following PR (n = 37)**	**3 Months After PR (n = 22)**	***p***
6MST (steps), median (IQR)	179 (113–209)	183 (160 to 273)		<0.01
Baseline MoCA <26	148 (103 to 202)	182 (121 to 310)		<0.01
Baseline MoCA ≥26	191 (156 to 246)	218 (162 to 263)		0.03
Between group *p*	0.08	0.03		
6MWT (meters), mean (SD)	386 (115)	418 (108)		0.01
Baseline MoCA <26	377 (117)	405 (116)		0.10
Baseline MoCA ≥26	409 (112)	443 (88)		0.08
Between group *p*	0.39	0.37		
HAD-Anxiety, mean (SD)	10 (4)	8 (4)	8 (4)	0.59
Baseline MoCA <26	10 (4)	9 (4)	9 (4)	0.67
Baseline MoCA ≥26	9 (5)	7 (3)	6 (3)	0.68
Between group *p*	0.42	0.12	0.14	
HAD-Depression, mean (SD)	8 (3)	7 (4)	6 (3)	0.17
Baseline MoCA <26	8 (3)	7 (4)	7 (4)	0.45
Baseline MoCA ≥26	7 (4)	6 (4)	6 (3)	0.78
Between group p	0.53	0.62	0.79	
SGRQ (%) – total score, mean (SD)	58 (16)	51 (14)	51 (14)	0.11
Baseline MoCA <26	62 (15)	53 (13)	54 (14)	0.11
Baseline MoCA ≥26	46 (15)	47 (15)	41 (12)	0.47
Between group *p*	< 0.01	0.19	0.09	
SGRQ (%) – symptom sub-score, mean (SD)	54 (22)	50 (20)	47 (20)	0.57
Baseline MoCA <26	56 (21)	46 (21)	48 (21)	0.73
Baseline MoCA ≥26	50 (24)	57 (17)	43 (18)	0.95
Between group *p*	0.35	0.14	0.66	
SGRQ (%) – activity sub-score, median (IQR)	77 (60 to 91)	73 (56 to 86)	73 (60 to 86)	0.85
Baseline MoCA <26	80 (65 to 93)	73 (60 to 86)	74 (61 to 86)	0.51
Baseline MoCA ≥26	65 (52 to 81)	66 (54 to 80)	60 (57 to 76)	0.54
Between group *p*	0.02	0.17	0.09	
SGRQ (%) – impact sub-score, median (IQR)	46 (39 to 62)	43 (24 to 55)*	39 (32 to 46)*ǂ	0.02
Baseline MoCA <26	51 (42 to 66)	45 (33 to 56)	43 (33 to 47)*	0.03
Baseline MoCA ≥26	39 (20 to 46)	33 (15 to 54)	37 (11 to 39)	0.73
Between groups *p*	<0.01	0.13	0.09	

Notes: Repeated ANOVA and Tukey post hoc tests or Friedman test and Wilcoxon as a post hoc test for pairwise comparison for within-group comparison. Mann–Whitney or independent *t*-test for between-group comparison. *Significantly different from baseline, p<0.05. ǂSignificantly different from following PR, p<0.05

Abbreviations: PR, pulmonary rehabilitation; 6MST, six-minute stepper test; 6MWT, six-minute walk test; HAD, anxiety and depression scale; SGRQ, Saint Georges Respiratory Questionnaire.

Discussion

The present study revealed that mild cognitive dysfunction was highly prevalent among people with severe to very severe COPD referred for PR (about 75%) but may not affect the benefits of PR since there was no statistical or clinically relevant difference in outcomes between those people with or without mild cognitive dysfunction. In addition, PR had the potential to improve short and mid-term cognitive function, particularly for those people who experienced mild cognitive dysfunction at the time they were referred to PR. Finally, mild cognitive dysfunction was not associated with a worst rate of exercise maintenance following PR nor with a worst rate of usability of a telemonitoring system.

Cognitive Function and Pulmonary Rehabilitation

The prevalence of mild cognitive dysfunction was relatively high in the present cohort (73%) compared with previous studies which also used the MoCA score as a screening tool (from 10% to 18%).[16,17] This difference may be explained by the severity of the subjects recruited since the worsening of the respiratory function and/or chronic hypoxia (48% of long-term users) have been associated with cognitive dysfunction.[43–46] The present results extend those from previous studies showing a positive effect of PR on cognitive function[19,20,47] particularly for those people who experienced mild cognitive dysfunction when attending PR. The physiological explanation underlying this improvement remains unclear but may include repetitive acute bouts of exercise sessions which contribute to increasing cardiac output and neurotransmitters release during exercise,[48] benefit of social exchanges during group exercise sessions as well as PR-induced neural changes.[49]

An additional important finding was that this positive effect was subsequently maintained 3 months following PR. Contrary to Emery et al, who found that the improvement in cognitive function was maintained at 1 year following PR only for those people who continued with a regular program of moderate-intensity exercise,[21] we did not find such an association, suggesting a residual effect of the initial program on cognitive function up to 3 months. This is of interest since this period is a hinge between the supervised program and the less or unsupervised long-term maintenance program which requires a cognitive function-directed behavior change. Though the preliminary results of this study suggest that cognitive dysfunction may not negatively affect exercise maintenance following PR, this should further be studied.

On the other hand, in the absence of a known minimal clinical important difference (MCID) for the MoCA score and considering than both the median score remained below 26 and the proportion of subjects with mild cognitive impairment did not significantly change during the follow-up period, the clinical relevance of the present findings remains questionable. Therefore, further study should consider to assess the MCID for the MoCA score, which offers the advantage to be easier to perform in clinical practice than more comprehensive cognitive function battery tests.

Impact of Cognitive Functions on PR Outcomes

Following PR, both those people with or without mild cognitive dysfunction significantly and clinically improved their performance on the 6MST (>20 steps[50]). The between-group difference following PR probably reflects the trend observed at baseline towards a lower performance for those people with mild cognitive dysfunction (p=0.08) so that the actual difference in improvement between groups is likely clinically trivial. In addition, the mean improvement in the 6MWT also lied within the range of the established MCID (25 to 33 m[39]) for the total population (p=0.01) and both subgroups. However, the latter failed to reach statistical significance due to a loss in statistical power. Contrary to Emery et al, we did not find any improvement in psychological wellbeing[19,20] but found a clinical improvement (>4 points[37]) in the SGRQ impact sub-score following and 3 months after PR, particularly in those people having a baseline mild cognitive dysfunction. In addition, neither the baseline MoCA score nor the change in the MoCA score was significantly associated with outcomes changes following PR. Altogether, these results extend those from a previous study[18] and suggest that cognitive dysfunction may not alter the progression during PR when subjects are closely supervised.

Implication for Practice and Research

Though cognitive dysfunction may not impede the effectiveness of supervised PR, the access to such programs is limited.[22–24] To cope with this difficulty, PR may be delivered in the home environment but this often implies a lower level of supervision.[51,52] Alternatively, home-based PR may provide supervision that center-based pulmonary rehabilitation provides if it uses new technologies to allow remote telemonitoring and therapists' prompt feedback. Reassuringly, this study provides preliminary evidence than people with mild cognitive dysfunction are able to use user-friendly telemonitoring system (83% were autonomous at the first session after initiation which was not significantly different from those people without mild cognitive dysfunction (71%, p=0.60) and within the range of the success rate of the overall cohort (86%)[34]). Since memory was significantly improved following PR in the present study, this strengthens the idea that subjects should be able to keep using this system throughout the program. Therefore, future studies should now assess the feasibility, safety and

effectiveness of a telemonitoring home-based PR for those people with COPD-related mild cognitive dysfunction.

Limits of the Study

The main limitations of this study were the lack of a control group without PR and the small sample size studied. In addition, the dropout rate was relatively high but comparable to the rate in other studies about PR.[52–54] However, those people who did not complete PR or did not attend the 3-month follow-up did not significantly differ from those who completed the overall study, suggesting a lack of selection bias. Nonetheless, this high attrition contributed to decreasing the power of the study which may have led to some type 2 statistical errors. Therefore, the lack of difference between those subjects with or without mild cognitive dysfunction on PR outcomes or telehealth system usability should be considered as exploratory.

Conclusion

Mild cognitive dysfunction is highly prevalent among those people with severe to very severe COPD referred for PR (about three quarter) but may not affect the benefits of PR. PR may improve short and mid-term cognitive function, particularly for those people who experience mild cognitive dysfunction at the time they are referred to PR. Finally, mild cognitive dysfunction may not affect exercise maintenance following PR nor the usability of a user-friendly telemonitoring system.

Registration

The protocol was prospectively registered on www.clinicaltrials.gov (NCT03244137).

Abbreviations

CI, confidence intervals; COPD, chronic obstructive pulmonary disease; CPET, cardiopulmonary exercise testing; FEV1, forced expiratory volume in 1 s; MCID, minimal clinical important difference; MoCA, Montreal Cognitive Assessment tool; PR, pulmonary rehabilitation.

Data Sharing Statement

De-identified participant data published in the manuscript will be shared to searcher performing a meta-analysis on request. Data will be available after publication. Please, contact Tristan Bonnevie (rehabilitation@adir-hautenormandie.com) for query.

Ethics and Consent Statement

This prospective observational study was approved by the French Ethics Committee Ile de France 1 (2017-juin-14586 ND). Written consent was obtained from all subjects.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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Table S1. Comparison of demographic characteristics between those patients who were excluded or not.

Characteristics	Patients			Between-group comparison
	Total (n = 56)	Excluded (n = 19)	Not excluded (n = 37)	*p*
Gender, n female (%)	30 (54)	12 (63)	18 (49)	0.40
Age *(yr)*, mean (SD)	62 (9)	62 (9)	63 (9)	0.72
Height *(cm)*, mean (SD)	165 (8)	164 (9)	165 (7)	0.68
Body-mass *(kg)*, mean (SD)	67 (17)	67 (21)	67 (15)	0.98
Body mass index *(kg/m²)*, mean (SD)	24.5 (5.2)	24.6 (6.5)	24.5 (4.6)	0.94
FEV_1 *(L)*, mean (SD)	0.9 (0.3)	0.8 (0.3	1.0 (0.4)	0.08
FEV_1 *(%)*, mean (SD)	37 (12)	34 (11)	39 (12)	0.17
FVC *(L)*, mean (SD)	2.3 (0.8)	2.2 (0.7)	2.4 (0.8)	0.19
FVC *(%)*, mean (SD)	75 (19)	71 (19)	77 (18)	0.32
FEV_1/FVC *(%)*, mean (SD)	41 (10)	40 (12)	41 (9)	0.74
Residual volume *(L)*, mean (SD)	4.1 (1.3)	4.2 (1.4)	4.1 (1.3)	0.72
Residual volume *(%)*, mean (SD)	193 (70)	209 (77)	184 (65)	0.23
TLC *(L)*, mean (SD)	6.6 (1.4)	6.4 (1.4)	6.7 (1.5)	0.48
TLC *(%)*, mean (SD)	120 (22)	121 (27)	120 (19)	0.81
VO_{2peak} *(ml/kg/min)*, mean (SD)	12 (3)	12 (3)	13 (4)	0.41
W_{peak} *(W)*, median (IQR)	50 (39 to 63)	50 (40 to 60)	50 (33 to 70)	1.00
6MST *(steps)*, mean (SD)	173 (67)	167 (56)	175 (72)	0.73
6MWT *(meters)*, mean (SD)	386 (115)	377 (127)	391 (110)	0.70
BODE index, mean (SD)	5 (2)	5 (2)	5 (2)	0.53
Long-term oxygen, n (%)	27 (48)	8 (42)	19 (51)	0.58
Home non-invasive ventilation, n (%)	7 (13)	3 (16)	4 (11)	0.68
HAD-Anxiety, mean (SD)	10 (4)	11 (5)	8 (4)	0.07
HAD-Depression, median (SD)	8 (5 to 10)	8 (4 to 10)	8 (5 to 10)	0.94
Saint Georges Respiratory Questionnaire *(%)*, median (IQR)	57 (51 to 65)	61 (52 to 82)	56 (4 to 62)	0.07
MoCA, median (IQR)	22 (20 to 26)	22 (20 to 25)	22 (22 to 26)	0.71

Fisher test for categorial data. Mann-Whitney or independent t-test for other characteristics.
Percentages may not sum to 100 due to rounding.

FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, VO_{2peak}

= maximal oxygen consumption, W_{peak} = maximal workload achieved during cardiopulmonary exercise testing, 6MWT = six-minute walk test, 6MST = six-minute stepper test, BODE = body-mass index, obstructive, dyspnea and exercise capacity index, HAD = anxiety and depression scale, MoCA = Montreal Cognitive Assessment tool.

Table S2. Comparison of demographic characteristics between those patients who attended the 3 months follow-up or not.

Characteristics	Patients			Between-group comparison
	Total (n = 37)	Dit not attend (n = 15)	Attended (n = 22)	*p*
Gender, n female (%)	18 (49)	8 (53)	10 (46)	0.74
Age *(yr)*, mean (SD)	63 (9)	63 (9)	63 (10)	0.97
Height *(cm)*, mean (SD)	165 (7)	162 (5)	167 (7)	0.05
Body-mass *(kg)*, mean (SD)	67 (15)	64 (16)	69 (13)	0.38
Body mass index *(kg/m²)*, mean (SD)	24.5 (4.6)	24.3 (5.4)	24.6 (4.1)	0.85
FEV_1 *(L)*, mean (SD)	1.0 (0.4)	0.9 (0.3)	1.1 (0.4)	0.26
FEV_1 *(%)*, mean (SD)	39 (12)	37 (13)	40 (13)	0.55
FVC *(L)*, mean (SD)	2.4 (0.8)	2.3 (0.7)	2.5 (0.8)	0.29
FVC *(%)*, mean (SD)	77 (18)	76 (20)	78 (18)	0.76
FEV_1/FVC *(%)*, mean (SD)	41 (9)	41 (8)	42 (9)	0.74
Residual volume *(L)*, mean (SD)	4.1 (1.3)	4.1 (0.9)	4.0 (1.5)	0.83
Residual volume *(%)*, mean (SD)	184 (65)	204 (52)	170 (70)	0.15
TLC *(L)*, mean (SD)	6.7 (1.5)	6.5 (0.8)	6.8 (1.8)	0.55
TLC *(%)*, mean (SD)	120 (19)	125 (22)	116 (19)	0.25
VO_{2peak} *(ml/kg/min)*, mean (SD)	13 (4)	13 (4)	12 (4)	0.45
W_{peak} *(W)*, mean (SD)	53 (24)	52 (22)	54 (26)	0.87
6MST *(steps)*, mean (SD)	175 (72)	151 (46)	189 (81)	0.18
6MWT *(meters)*, mean (SD)	391 (110)	392 (115)	390 (111)	0.97
BODE index, mean (SD)	5 (2)	5 (1)	5 (2)	0.42
Long-term oxygen, n (%)	19 (51)	7 (47)	12 (55)	0.74
Home non-invasive ventilation, n (%)	4 (11)	3 (20)	1 (10)	0.28
HAD-Anxiety, mean (SD)	9 (4)	9 (4)	9 (4)	0.91
HAD-Depression, median (SD)	8 (5 to 10)	8 (5 to 12)	8 (5 to 9)	0.47
Saint Georges Respiratory Questionnaire *(%)*, mean (SD)	54 (15)	53 (15)	54 (15)	0.80
MoCA, median (IQR), baseline	22 (22 to 26)	25 (19 to 27)	22 (20 to 26)	0.33
MoCA, mean (SD), following PR	24 (3)	23 (3)	24 (3)	0.38

Fisher test for categorial data. Mann-Whitney or independent t-test for other characteristics.
Percentages may not sum to 100 due to rounding.

FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, VO_{2peak} = maximal oxygen consumption, W_{peak} = maximal workload achieved during cardiopulmonary exercise testing, 6MWT = six-minute walk test, 6MST = six-minute stepper test, BODE = body-mass index, obstructive, dyspnea and exercise capacity index, HAD = anxiety and depression scale, MoCA = Montreal Cognitive Assessment tool, PR = pulmonary rehabilitation.

Table S3. Comparison of demographic characteristics between those patients with a baseline MoCA < 26 who were excluded or not.

Characteristics	Patients			Between-group comparison
	MoCA < 26 (n = 41)	Excluded (n = 16)	Not excluded (n = 25)	*p*
Gender, n female (%)	20 (49)	9 (56)	11 (44)	0.53
Age *(yr)*, mean (SD)	64 (9)	62 (9)	64 (8)	0.51
Height *(cm)*, mean (SD)	165 (8)	165 (10)	165 (6)	0.83
Body-mass *(kg)*, mean (SD)	68 (18)	70 (21)	67 (15)	0.55
Body mass index *(kg/m²)*, mean (SD)	25 (5.5)	25.7 (6.4)	24.5 (5)	0.48
FEV_1 *(L)*, mean (SD)	0.9 (0.6 to 1.2)	0.8 (0.3)	1.0 (0.4)	0.13
FEV_1 *(%)*, mean (SD)	36 (28 to 44)	33 (11)	39 (13)	0.20
FVC *(L)*, mean (SD)	2.2 (1.6 to 2.7)	2.1 (0.8)	2.4 (0.8)	0.28
FVC *(%)*, mean (SD)	73 (19)	70 (19)	76 (19)	0.30
FEV_1/FVC *(%)*, mean (SD)	41 (10)	40 (12)	42 (9)	0.72
Residual volume *(L)*, mean (SD)	4.2 (1.3)	4.4 (1.3)	4.1 (1.4)	0.50
Residual volume *(%)*, mean (SD)	194 (73)	216 (77)	178 (68)	0.13
TLC *(L)*, mean (SD)	6.7 (1.4)	6.6 (1.3)	6.7 (1.5)	0.72
TLC *(%)*, mean (SD)	121 (22)	123 (25)	120 (19)	0.69
VO_{2peak} *(ml/kg/min)*, mean (SD)	12 (3)	11 (3)	12 (4)	0.59
W_{peak} *(W)*, median (IQR)	45 (36 to 60)	50 (40 to 60)	40 (30 to 60)	0.49
6MST *(steps)*, mean (SD)	148 (103 to 202)	154 (46)	166 (79)	0.72
6MWT *(meters)*, mean (SD)	377 (117)	369 (120)	382 (118)	0.77
BODE index, mean (SD)	5 (2)	6 (2)	5 (2)	0.46
Long-term oxygen, n (%)	22 (54)	8 (50)	14 (56)	0.76
Home non-invasive ventilation, n (%)	6 (15)	3 (19)	3 (12)	0.66
HAD-Anxiety, mean (SD)	10 (4)	11 (5)	9 (4)	0.28
HAD-Depression, mean (SD)	8 (3)	8 (3)	8 (3)	0.48
Saint Georges Respiratory Questionnaire *(%)*, mean (SD)	62 (15)	68 (16)	57 (13)	0.03
MoCA, mean (SD)	21 (2)	22 (2)	21 (2)	0.47

Fisher test for categorial data. Mann-Whitney or independent t-test for other characteristics.
Percentages may not sum to 100 due to rounding.

MoCA = Montreal Cognitive Assessment tool, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, VO_{2peak} = maximal oxygen consumption, W_{peak} = maximal workload achieved during cardiopulmonary exercise testing, 6MWT = six-minute walk test, 6MST = six-minute stepper test, BODE = body-mass index, obstructive, dyspnea and exercise capacity index, HAD = anxiety and depression scale.

Table S4. Comparison of demographic characteristics between those patients with a baseline MoCA < 26 who attended the 3 months follow-up or not.

Characteristics	Patients			Between-group comparison
	Total (n = 25)	Dit not attend (n = 8)	Attended (n = 17)	*p*
Gender, n female (%)	11 (44)	4 (50)	7 (41)	1.00
Age *(yr)*, mean (SD)	64 (8)	67 (5)	63 (9)	0.36
Height *(cm)*, mean (SD)	165 (6)	161 (3)	167 (7)	<0.01
Body-mass *(kg)*, mean (SD)	67 (15)	64 (18)	68 (15)	0.54
Body mass index *(kg/m²)*, mean (SD)	24.5 (5)	24.6 (6.1)	24.4 (4.6)	0.95
FEV_1 *(L)*, mean (SD)	1.0 (0.4)	0.8 (0.3)	1.1 (0.4)	0.14
FEV_1 *(%)*, mean (SD)	39 (13)	36 (12)	40 (14)	0.44
FVC *(L)*, mean (SD)	2.4 (0.8)	2.1 (0.6)	2.6 (0.8)	0.14
FVC *(%)*, mean (SD)	76 (19)	73 (20)	78 (19)	0.57
FEV_1/FVC *(%)*, mean (SD)	42 (9)	41 (9)	42 (9)	0.86
Residual volume *(L)*, mean (SD)	4.1 (1.4)	4.1 (0.9)	4.1 (1.6)	0.92
Residual volume *(%)*, mean (SD)	178 (68)	197 (49)	169 (75)	0.40
TLC *(L)*, mean (SD)	6.7 (1.5)	6.3 (0.7)	6.9 (1.8)	0.39
TLC *(%)*, mean (SD)	120 (19)	123 (21)	119 (19)	0.66
VO_{2peak} *(ml/kg/min)*, mean (SD)	12 (4)	12 (4)	12 (4)	0.82
W_{peak} *(W)*, mean (SD)	48 (19)	45 (14)	49 (21)	0.64
6MST *(steps)*, mean (SD)	166 (79)	129 (43)	181 (86)	0.22
6MWT *(meters)*, mean (SD)	382 (118)	337 (129)	396 (114)	0.34
BODE index, median (IQR)	7 (5 to 7)	5 (3 to 6)	5 (4 to 7)	0.16
Long-term oxygen, n (%)	14 (56)	5 (63)	9 (53)	1.00
Home non-invasive ventilation, n (%)	3 (12)	2 (25)	1 (6)	0.23
HAD-Anxiety, mean (SD)	9 (4)	10 (4)	9 (3)	0.65
HAD-Depression, mean (SD)	8 (3)	6 (3)	7 (4)	0.64
Saint Georges Respiratory Questionnaire *(%)*, median (IQR)	58 (52 to 64)	59 (49 to 63)	57 (52 to 65)	0.86
MoCA, mean (SD)	21 (2)	21 (3)	31 (2)	0.53

Fisher test for categorial data. Mann-Whitney or independent t-test for other characteristics.
Percentages may not sum to 100 due to rounding.

MoCA = Montreal Cognitive Assessment tool, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, TLC = total lung capacity, VO_{2peak} = maximal oxygen consumption, W_{peak} = maximal workload achieved during cardiopulmonary exercise testing, 6MWT = six-minute walk test, 6MST = six-minute stepper test, BODE = body-mass index, obstructive, dyspnea and exercise capacity index, HAD = anxiety and depression scale.

I.6. Discussion et conclusion de la première partie

La BPCO est une pathologie respiratoire chronique menant progressivement à une situation de handicap ventilatoire.

La réhabilitation respiratoire est efficace pour lutter contre les conséquences « systémiques » de la BPCO. Cependant très peu de patients peuvent en bénéficier, notamment à cause du faible nombre de places disponibles dans les centres d'évaluation (pour réaliser l'épreuve d'effort cardiorespiratoire) ainsi que dans les centres de réhabilitation eux-mêmes. Un modèle alternatif visant à élargir l'offre de réhabilitation à plus large échelle consisterait à évaluer et réhabiliter les patients hors des centres de réhabilitation.

Ainsi, le test stepper de 6 minutes est proposé comme alternative à l'épreuve d'effort afin de prescrire l'intensité de l'entrainement en endurance et du renforcement musculaire. Dans un premier temps, nos deux travaux de recherche se sont intéressés à la prescription de l'intensité de l'entrainement en endurance.

Tout en reconnaissant ses limites liées à son caractère rétrospectif et son faible effectif, notre première étude (108) a révélé des résultats encourageants en retrouvant 1) une relation significative forte entre la fréquence cardiaque des trois premières minutes du test stepper de 6 minutes et la fréquence cardiaque au seuil ventilatoire obtenue au cours de l'épreuve d'effort incrémentale cardiorespiratoire ($r=0.69$, $p=0.001$) ainsi que 2) une relation significative forte entre le nombre de pas réalisés durant le test stepper de 6 minutes et la puissance au seuil ventilatoire ($r=0.59$, $p<0.01$). Cette piste a été approfondie dans un second temps via une étude prospective multicentrique qui retrouve des résultats similaires. Ainsi, un modèle statistique multivarié ne retrouve que deux facteurs prédictifs indépendant de la fréquence cardiaque au

seuil ventilatoire (moyenne de fréquence cardiaque sur les trois premières minutes du test stepper de 6 minutes ainsi que l'âge) permettant néanmoins d'expliquer plus d'un tiers de la variance de la fréquence cardiaque au seuil ventilatoire (r^2=0.38, p<0.01). L'analyse visant à prédire la puissance au seuil ventilatoire ne retrouve qu'un seul facteurs prédictif indépendant (nombre de pas au cours du test stepper de 6 minutes) expliquant à lui seul près de la moitié de la variance (r^2=0.48, p<0.01). Ces donnée ssuggérent que le test stepper de 6 minutes peut être utilisé pour prescrire l'intensité de l'entrainement en endurance chez les patients présentant une forme légère à modérée de BPCO. Ces résultats doivent être discutés au regard des limites inhérentes de cette étude. Tout d'abord, l'effectif reste faible malgré une période d'inclusion relativement large (plusieurs années sur deux centres). Cet effectif reflète les difficultés d'accès aux programmes de réhabilitation des patients peu sévères qui ne sont pas considérés comme prioritaires en raison du nombre restreint de places disponibles en centre, aussi bien pour l'évaluation que pour la réalisation du programme de réhabilitation lui-même. Malgré le faible effectif, cette étude a permis le développement d'une équation valide (au sein de ce groupe) pour la prescription de l'entrainement en endurance dans cette population. La validité de cette équation n'a pas été confirmée dans un groupe de validation externe dont la fréquence cardiaque était monitorée de façon plus proche de la pratique courante (mesure ponctuelle de la fréquence cardiaque) et présentant des caractéristiques trop différentes de la population initiale (particulièrement un indice de masse corporel supérieur). Aussi, la validité externe de ces équations est limitée et leur utilisation devrait se limiter à des patients dont le poids est inférieur à 90 kg et ayant été évalués avec un monitorage continu de la fréquence cardiaque.

Afin d'envisager la prescription d'un programme de réentrainement complet (incluant exercice en endurance et renforcement musculaire) à partir d'un test unique, nous avons mené une étude préliminaire utilisant le même test que les deux études précédentes (test stepper de 6 minutes) ciblant la prescription du renforcement musculaire (109). Bien que nos résultats

retrouvent une relation modérée entre le nombre de pas réalisés au cours du test stepper de 6 minutes et la 1RM ($r=0.41$, $p<0.01$), le modèle prédictif de prescription entrainerait une erreur de 30 kg. Ainsi, malgré ses limites (la principale étant son caractère rétrospectif), nous avons montré que l'utilisation du test stepper pour prescrire le renforcement musculaire périphérique (en particulier celui du muscle quadriceps) entrainait une erreur qui n'est cliniquement pas acceptable. De plus, cette erreur est telle qu'il est peu probable qu'un travail méthodologiquement plus robuste apporte des résultats substantiellement différents et puisse conduire à une utilisation valide de ce test pour prescrire le renforcement musculaire périphérique. Aussi, nous n'avons pas poursuivi les travaux de recherche dans cette direction.

Au total, nos travaux menés dans l'objectif d'utiliser le test stepper de 6 minutes pour faciliter l'évaluation des patients montrent que celui-ci pourrait être utilisé pour prescrire l'entrainement en endurance des patients présentant une forme légère à modérée de BPCO. Néanmoins, la validité externe de ces résultats doit être discutée dans la mesure où le test ne peut être proposé qu'à des patients dont le poids serait inférieur à 90 kg et ne présentant pas de troubles de l'équilibre.

Après avoir proposé une modalité d'évaluation simplifiée pour les patients adressés en réhabilitation respiratoire, nous nous sommes interrogés sur la possibilité de délocaliser le réentrainement au domicile tout en permettant un niveau de supervision équivalent à celui proposé en centre, à travers l'utilisation des technologies de santé. Dans une étude prospective observationnelle multicentrique, nous avons d'abord établi la faisabilité (86% des patients sont autonomes pour utiliser le dispositif dès la première session [95% IC 78 à 92%]), la fiabilité (données transmises au cours de 98% des séances et présentant moins de 1% d'artefact ; similarité clinique entre les données transmises et les données locales à 99% pour la fréquence cardiaque et 100% pour la saturation transcutannée en oxygène) et montré que la technique était

bien acceptée par les participants (plus de 95% des patients sont satisfaits ou très satisfaits, considèrent le dispositif facile à utiliser et seraient prêts à l'utiliser pour réaliser un programme de réhabilitation à domicile) (110). La principale force de cette étude est qu'elle a été systématiquement proposée à tous les patients adressés en réhabilitation dans notre centre, conférant aux résultats une forte validité externe. Plus de 65 000 données appariées ont ainsi pu être analysées, ce qui renforce la confiance que nous pouvons avoir dans les estimations des marges d'erreur retrouvées.

Une limite de notre étude est qu'elle n'avait pas prévu l'évaluation des fonctions cognitives, pourtant impliquées dans l'utilisation de ces technologies de santé. Par ailleurs, l'altération des fonctions cognitives pourrait également compromettre le modèle de réhabilitation à domicile sans supervision. C'est pour cette raison que nous avons réalisé une étude prospective multicentrique, afin d'évaluer la prévalence des dysfonctions cognitives parmi les patients adressés en réhabilitation (111). Notre étude fait un état des lieux sur un sujet jusqu'alors peu exploré, et permet de décrire la forte prévalence de la dysfonction cognitive parmi les patients adressés en réhabilitation respiratoire dans le cadre d'une BPCO (73% [95% IC 60 à 83%]). Grâce à l'inclusion de patients ayant pu participer conjointement à nos deux études, ces résultats permettent de faire le lien avec l'utilisation des technologies de santé lors d'un programme de réhabilitation à domicile. Ainsi, la présence d'une dysfonction cognitive ne semble pas influencer l'utilisation et les résultats fournis par un dispositif de telemonitoring (83% des patients avec dysfonction cognitive sont autonomes dès la première séance comparé à 71% des patients sans dysfonction cognitive, p=0.60) ni les bénéfices acquis au cours d'un programme de réhabilitation supervisé en terme de capacités physique (test de marche de 6 minutes et test stepper de 6 minutes), de qualité de vie (Saint George's Respiratory Questionnaire) ou encore de bénéfices psychologiques (Hospital Anxiety and Depression scale). Ces résultats sont à interpréter avec précaution en raison du faible effectif de notre étude ainsi

que des nombreux abandons qui soulèvent la possibilité d'une erreur statistique de type 2. Ainsi, les bénéfices physiques, psychologiques et l'amélioration de la qualtié de vie des patients présentant une dysfonction cognitive ainsi que leur capacité à utiliser des dispositifs de telemonitoring méritent d'être confirmés dans de futurs travaux de recherche, lorsqu'ils sont adressés en réhabilitation non ou peu supervisée (au domicile par exemple).

Au total, les contributions originales de cette première partie montrent qu'un modèle alternatif, constitué des évaluations des patients et des conduites optimisées de réhabilitation en dehors des centres, est désormais possible. La prévalence élevée des troubles cognitifs parmi les patients adressés en réhabilitation respiratoire nécessite toutefois de confirmer la faisabilité du réentrainement à domicile pour cette population. En pratique, le test stepper de 6 minutes peut être réalisé en cabinet de kinésithérapie ou au domicile des patients pour prescrire l'intensité de l'entrainement en endurance pour les patients peu sévères. Néanmoins, cela ne s'applique pas pour le renforcement musculaire. Une fois l'évaluation réalisée, la réhabilitation peut se dérouler à domicile en offrant un niveau de supervision équivalent à celle d'un centre grâce aux outils de telemonitoring (oxymétrie en particulier). L'utilisation de tels dispositifs est faisable, même pour les patients présentant une dysfonction cognitive, est acceptée par les patients et permet la transmission de données valides.

Les futures études doivent poursuivre l'évaluation du test stepper de 6 minutes pour prescrire l'intensité de l'entrainement en endurance pour des patients plus sévères dont le suivi à domicile pourrait également être assuré grâce au telemonitoring. La possibilité d'intégrer le suivi de la performance des patients au cours des séances grâce au telemonitoring devrait également être évaluée afin d'améliorer leur suivi en complétant les algorithmes de détection des exacerbations et permettre un traitement précoce de celles-ci (77, 112-115). Des stratégies

alternatives doivent encore être développées afin de faciliter l'évaluation et la prescription du renforcement musculaire. Enfin, la faisabilité de ce modèle pour les patients présentant une dysfonction cognitive nécessite d'être évaluée.

Seconde partie

II. Outils existants et nouveaux outils pour optimiser les effets du réentrainement à l'exercice

Rationnel et généralités sur les adjuvants au réentrainement à l'exercice

Ventilation non invasive à l'effort : impact de l'interface, des asynchronismes patient-ventilateur et de la performance du ventilateur

Utilisation de l'électrostimulation excito-motrice ou antalgique pour optimiser les effets du réentrainement à l'exercice

Bonnevie T, Gravier FE, Debeaumont D, Viacroze C, Muir JF, Cuvelier A, et al. Home-based Neuromuscular Electrical Stimulation as an Add-on to Pulmonary Rehabilitation Does Not Provide Further Benefits in Patients With Chronic Obstructive Pulmonary Disease: A Multicenter Randomized Trial. Arch Phys Med Rehabil. 2018;99(8):1462-70.

Bonnevie T, Gravier FE, Prieur G, Combret Y, Debeaumont D, Patout M, et al. Lumbar transcutaneous electrical nerve stimulation to improve exercise performance in COPD patients. Eur Respir J 2019;54(6).

Bonnevie T, Gravier FE, Fresnel E, Kerfourn A, Medrinal C, Prieur G, et al. NIV is not adequate for high intensity endurance exercise in COPD. J Clin Med 2020;9(4):1054.

II.1. Rationnel et généralités sur les adjuvants au réentrainement à l'exercice

La question de l'efficacité de la réhabilitation respiratoire semble avoir trouvé une réponse positive depuis la dernière méta-analyse conduite par l'association *Cochrane* (40). Néanmoins, cette question laisse place à de nombreuses autres, en particulier celle de la modalité d'entrainement à l'exercice la plus efficace.

L'entrainement en endurance peut être réalisé selon différentes modalités : entrainement en plateau ou par intervalle. A ce jour, les données scientifiques ne permettent de conclure à la supériorité d'une approche plutôt que l'autre (47). Malgré cela, que l'entrainement soit réalisé en plateau ou par intervalle, les analyses physiologiques semblent confirmer l'intérêt d'un entrainement à haute intensité (116-118). Paradoxalement, la plupart des patients ne tolèrent pas un tel entrainement en raison de leur limitation ventilatoire et de la dyspnée (118). Aussi, les stratégies actuelles pour optimiser les effets du réentrainement visent à :

1. diminuer la dyspnée pour permettre une sollicitation musculaire plus importante durant les séances d'entrainement,
2. permettre un travail musculaire périphérique supplémentaire avec une stimulation cardiorespiratoire réduite en dehors des séances.

Afin de répondre à ces objectifs, plusieurs outils ont été proposés et sont considérés comme des adjuvants à la réhabilitation respiratoire. Parmi eux, figurent la ventilation non invasive au cours de l'effort ou encore l'électrostimulation.

L'intérêt de la ventilation non-invasive au cours de l'effort est étudié depuis plusieurs années mais reste controversé (119, 120). Cela s'explique par le fait que l'efficacité de cet outil dépend de nombreux facteurs dont l'influence reste mal connue.

L’efficacité de l’électrostimulation musculaire excito-motrice du quadriceps est quant à elle relativement bien décrite dans la prise en charge des patients atteints de BPCO sévère, particulièrement ceux présentant un handicap ventilatoire trop important pour participer à un programme de réhabilitation respiratoire (121, 122). Cela s’explique par le fait que cette modalité de stimulation musculaire est associée à un coût énergétique métabolique plus faible que la contraction musculaire volontaire, diminuant ainsi la dyspnée des patients (123, 124). Néanmoins, il existe peu de données concernant l’évaluation de l’électrostimulation musculaire excito-motrice utilisée comme adjuvant à la réhabilitation respiratoire (c’est-à-dire en plus des séances de réentrainement à l’exercice).

Enfin, l’électrostimulation antalgique est une piste encore peu explorée qui pourrait permettre d’améliorer la tolérance à l’effort des patients.

II.2. Objectifs de la seconde partie

Les objectifs des contributions originales présentées dans cette seconde partie sont :

1. d'évaluer l'influence des interfaces, des asynchronismes patient-ventilateur ainsi que de la performance technologique du ventilateur lors de l'effort sous ventilation non invasive chez les patients atteints de BPCO,
2. d'évaluer les effets de l'électrostimulation excito-motrice du quadriceps en tant qu'adjuvant à la réhabilitation respiratoire,
3. D'évaluer les effets de l'électrostimulation antalgique au cours de l'effort chez les patients atteints de BPCO.

II.3. Ventilation non invasive à l'effort : impact des interfaces, des asynchronismes patient-ventilateur et de la performance du ventilateur

L'épidémie de poliomyélite qui a eu lieu dans les années 1950 au Danemark a eu pour conséquence de développer les techniques et l'organisation de la ventilation artificielle au long cours (125, 126). En France, la ventilation non invasive s'est développée dès les années 1990 grâce aux associations coordonnées par les centres hospitaliers universitaires, qui avaient été mises en place pour organiser le retour à domicile des patients trachéotomisés dans les suites de l'épidémie de poliomyélite et qui se sont occupés ensuite de la diffusion de l'oxygénothérapie à domicile dans la BPCO (126).

Dans le cadre de la BPCO, la ventilation non invasive à domicile répond à la dégradation de la fonction ventilatoire conduisant progressivement à une hypoventilation alvéolaire (diminution du volume d'air inspiré à chaque cycle respiratoire et/ou du nombre de cycles respiratoires par minute) et responsable d'une hypercapnie chronique elle-même associée à l'augmentation de la mortalité (14, 127). L'hypoventilation alvéolaire trouve son origine au cours du sommeil. Durant celui-ci, la réponse des centres respiratoires aux messages chimiques (chémorécepteurs) et mécaniques (mécanorécepteurs) est atténuée, diminuant ainsi la commande des muscles respiratoires (128). La diminution du tonus des muscles laryngés ainsi que des muscles respiratoires accessoires au cours du sommeil entraine respectivement une augmentation des résistances des voies aériennes ainsi qu'une hypoventilation alvéolaire (129). Le diaphragme n'est pas concerné par cette hypotonie, mais l'emphysème parfois présent au cours de la BPCO est responsable d'une distension thoracique qui réduit l'efficacité contractile du diaphragme (130). La réduction de la ventilation minute pulmonaire produit une diminution

du rapport entre la ventilation et la perfusion (responsable d'une hypoxémie et d'une hypercapnie) (128).

Afin d'augmenter la ventilation alvéolaire et traiter l'hypercapnie, la ventilation non invasive en pression positive à domicile s'est largement développée dans la plupart des pays européens (126). Le principe du traitement est de pressuriser les voies aériennes des patients de façon synchronisée avec leurs cycles inspiratoires ou/et expiratoires afin d'augmenter le volume courant tout en réduisant le travail des muscles respiratoires et améliorer ainsi les échanges gazeux (131). Par ailleurs la VNI permet d'améliorer la sensibilité des centres respiratoires à l'hypercapnie et l'hypoxémie, avec un effet rémanant sur la capnie diurne au cours du nycthémère. Les évolutions technologiques au cours des deux dernières décennies ont permis le développement de ventilateurs de domicile plus performants, tant sur les capacités de pressurisation que sur le monitoring respiratoire, ainsi que la multiplication d'interfaces de plus en plus confortables et adaptées à la morphologie des patients (132).

Il existe différents modes de ventilation. Le plus utilisé en France est le mode "spontanée avec fréquence de sécurité" soit "Spontaneous/Timed" ou "ST". Bien qu'il existe plusieurs réglages à paramétrer pour non seulement l'efficacité mais aussi le confort du traitement, les trois principaux sont :

- la pression inspiratoire, probablement le réglage le plus important car il permet de générer les volumes administrés au patient. Des pressions inspiratoires délivrées trop faibles ne permettent pas le contrôle de l'hypoventilation alvéolaire alors que des pressions trop élevées sont sources d'inconfort et de mauvaise observance, du fait en particulier de fuites sur le circuit et d'asynchronisme patient-ventilateur de déclenchement et de cyclage (133).
- la pression expiratoire permet de maintenir les voies aériennes ouvertes au cours du sommeil. Elle est également utile pour limiter le phénomène de rebreathing pour les

circuits monobranches à fuites intentionnelles. Son réglage se fait en prenant en compte les comorbidités des patients tels que leur statut cardio-vasculaire et la présence d'apnées obstructives ou centrales du sommeil.

- la fréquence de sécurité permet d'assurer au patient un nombre minimum de cycles respiratoires par minute. Un nombre de cycles est imposé par la machine et le patient ne peut respirer à un rythme inférieur à celui défini.

Les études contrôlées randomisées n'ont que récemment démontré le bénéfice de la VNI à domicile sur la survie des patients atteints de BPCO à long terme (134, 135), alors que les spécialistes européens de l'insuffisance respiratoire chronique avaient déja développé depuis longtemps cette indication parmi leurs patients les plus sévères (136). Il est désormais acquis que les patients répondeurs au traitement sont ceux ayant les niveaux de capnie diurne les plus élevés (PaCO2 diurne > 50mmHg ou PaCO2 nocturne > 55mmHg) à condition que la ventilation non invasive soit réglée selon le sprinciupes de la VNI de haute intensité, se rapprochant d'une ventilation contrôlée (fréquence de sécurité élevée, pressions inspiratoires élevées) (137).

La ventilation non invasive nocturne a d'abord été proposée au cours de la réhabilitation respiratoire chez les patients atteints d'une insuffisance respiratoire hypercapnique. En se basant sur les effets retrouvés au long cours, le postulat initial était que la ventilation non invasive nocturne pourrait améliorer les bénéfices de la réhabilitation respiratoire en mettant au repos et améliorant le métabolisme des muscles respiratoires, en améliorant la mécanique ventilatoire ainsi que la qualité du sommeil (138). Ainsi, plusieurs équipes ont montré que cette utilisation au cours d'un programme de réhabilitation permettait d'améliorer non seulement les

échanges gazeux, les biomarqueurs de l'inflammation, la fatigue, mais également l'activité physique objective des patients (nombre de pas par jour) (138, 139).

En parallèle, son utilisation a été étudiée spécifiquement au cours de l'exercice et ce, indépendamment de l'existence d'une hypercapnie diurne ou nocturne (119, 140, 141). Les différents modes de ventilation retrouvés dans la littérature pour une utilisation au cours de l'effort sont la pression positive continue, la ventilation assisstée proportionnelle et la pression positive en mode spontannée. Bien qu'il soit difficile de conclure quant au mode le plus efficace pour améliorer la tolérance à l'effort des patients, une meta-analyse semble donner l'avantage à la pression possitive en mode spontannée (comparaison indirecte) (142). Ainsi, l'objectif de la ventilation non invasive lors de l'exercice est de permettre aux patients de soutenir des intensités d'exercice plus importantes grâce à une diminution de la charge de travail des muscles respiratoires (143) et de soulager la dyspnée (144). Ainsi, lors d'un effort aigu à charge constante, plusieurs équipes ont pu objectiver une diminution de la charge de travail des muscles respiratoires (143, 145) ainsi qu'une amélioration de la saturation transcutannée en oxygène (146).

Grâce à la diminution du travail respiratoire, la ventilation non invasive pourrait permettre une redistribution du débit cardiaque (initialement destiné aux muscles respiratoires) vers les muscles locomoteurs (147) (**Figure 2**), diminuant ainsi leur fatigue (144, 148) et permettant aux patients de maintenir des intensités d'exercice plus élevées.

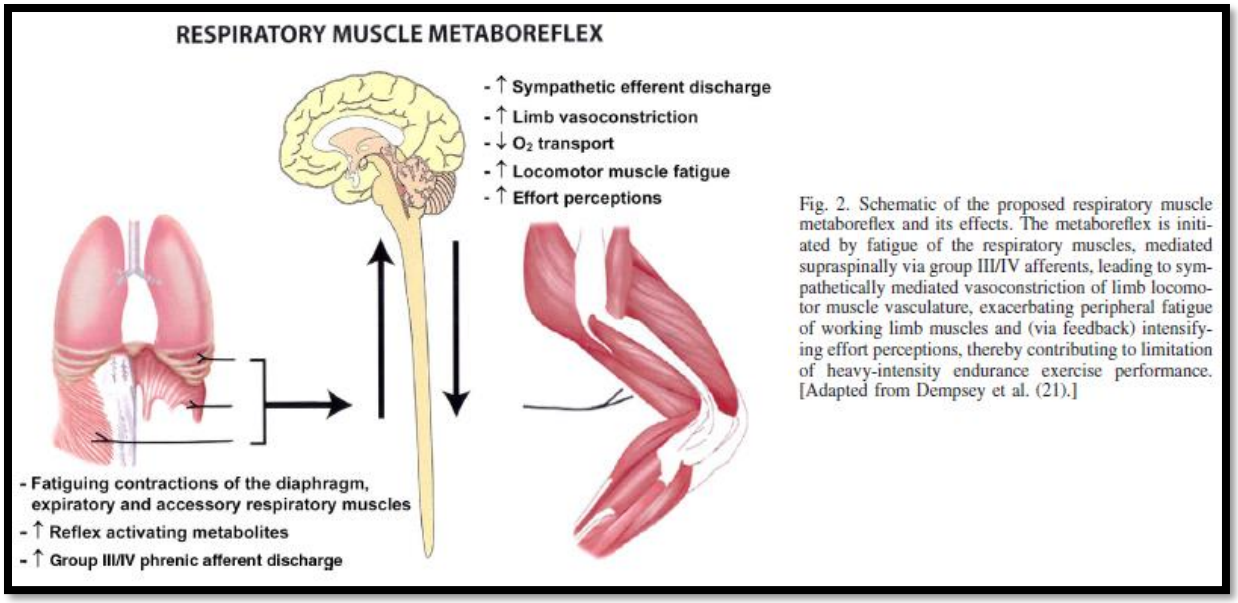

Figure 2 : *Schéma du métaboréflexe inhibiteur. Le métaboréflexe est initié par la fatigue des muscles respiratoires via les afférences supra spinales de groupe III/IV, entrainant une vasoconstriction dans les muscles locomoteurs liée à l'activité sympathique, exacerbant la fatigue périphérique des muscles à l'effort ainsi que l'intensité de la perception de l'effort, contribuant à la limitation de l'exercice (147).*

Ainsi, les bénéfices physiologiques apportés par la ventilation non invasive au cours d'un effort aigu se traduisent dans la majorité des études physiologiques par un bénéfice significatif en terme de capacité à l'exercice (142, 144, 149-151), bien que certains travaux ne confirment pas ces résultats (152, 153).

A l'inverse, les effets de l'utilisation répétée de la ventilation non invasive au cours des sessions d'exercice composant un programme de réhabilitation respiratoire restent incertains (119, 120, 141, 154) et nourrissent de nombreux débats. Afin de permettre un bénéfice au décours du programme de réhabilitation, il semble nécessaire que la ventilation non invasive soit au préalable utilisée de façon optimale durant chacune des séances. Néanmoins, son efficacité dépend de nombreux facteurs (mode de ventilation, paramètres de ventilation,

population ciblée, type d'interface, asynchronismes patient-ventilateur, performances technologiques du ventilateur) dont l'influence reste peu connue. L'objectif de la contribution originale proposée ci-dessous est donc d'évaluer l'influence de ces paramètres sur la performance à l'exercice des patients atteints de BPCO sévère à très sévère.

Étude n°6

Influence des interfaces, des asynchronismes patients-ventilateurs ainsi que de la performance technologique du ventilateur lors de l'effort sous ventilation non invasive chez les patients atteints de BPCO

NIV Is not Adequate for High Intensity Endurance Exercise in COPD

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NIV Is not Adequate for High Intensity Endurance Exercise in COPD

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Abstract: Noninvasive ventilation (NIV) during exercise has been suggested to sustain higher training intensity but the type of NIV interface, patient-ventilator asynchronies (PVA) or technological limitation of the ventilator may interfere with exercise. We assessed whether these parameters affect endurance exercise capacity in severe COPD patients. In total, 21 patients with severe COPD not eligible to home NIV performed three constant workload tests. The first test was carried out on spontaneous breathing (SB) and the following ones with NIV and a nasal or oronasal mask in a randomized order. PVA and indicators of ventilator performance were assessed through a comprehensive analysis of the flow pressure tracing raw data from the ventilator. The time limit was significantly reduced with both masks (406 s (197–666), 240 s (131–385) and 189 s (115–545), $p < 0.01$ for tests in SB, with oronasal and nasal mask, respectively). There were few PVA with an oronasal mask (median: 3.4% (1.7–5.2)) but the ventilator reached its maximal generating capacity (median flowmax: 208.0 L/s (189.5–224.8) while inspiratory pressure dropped throughout exercise (from 10.1 (9.4–11.4) to 8.8 cmH2O (8.6–10.8), $p < 0.01$). PVA were more frequent with nasal mask (median: 12.8% (3.2–31.6), $p < 0.01$). Particularly, the proportion of patients with ineffective efforts > 10% was significantly higher with nasal interface (0% versus 33.3%, $p < 0.01$). NIV did not effectively improve endurance capacity in COPD patients not acclimated to home NIV. This was due to a technological limitation of the ventilator for the oronasal mask and the consequence either of an insufficient pressure support or a technological limitation for the nasal mask.

Keywords: pulmonary disease; chronic obstructive pulmonary disease; noninvasive ventilation; exercise; patient-ventilator asynchronies

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and mortality worldwide [1]. Pulmonary rehabilitation (PR) has been proposed to manage its systemic effects and effectively increases functional capacity and quality of life (QoL) [2]. On the other hand, home-based noninvasive ventilation (NIV) effectively improves outcomes for those who experience diurnal hypercapnia (>55 mmHg) treated with high inspiratory pressure and rather high backup rate [3,4]. Nighttime NIV accompanying daytime PR has been suggested for these patients to improve general fatigue, gas exchanges and the benefits of PR [5,6]. In the context of a training session during PR, NIV has initially been studied during exercise, whether hypercapnia is present or not, as suggested by a recent systematic review [7] and an expert review [8]. The rationale for using NIV during exercise is based on physiologic studies supporting high intensity training [8,9]. As this might not be tolerable for most not hypercapnic patients [9], NIV is thought to relieve the work of breathing [10] and dyspnea [11]. NIV may also contribute to the redistribution of cardiac output from the respiratory muscles toward the exercising lower limb muscles, decreasing their fatigue [11], helping patients to sustain higher training stimuli, further improving the benefits of PR [7,12]. However, this notion has recently been questioned by Anekwe et al. who found that both patient-ventilator asynchrony and ventilator technological limitation may occur when patients reach high intensity during an incremental cardiopulmonary exercise testing [13]. As this test does not represent the usual training modality used during PR [14,15], their occurrence during a constant high intensity endurance exercise testing deserves to be studied. Moreover, the influence of the interface used remain unknown. Nasal or oronasal masks (NM and ONM, respectively) are used inconsistently across studies [16,17] and many patients stop training due to interface discomfort [16,18]. The choice of the interface is of real concern because the high level of ventilation during exercise necessitates breathing through the mouth, which in turn may elicit important leaks and patient-ventilatory asynchrony that would compromise exercise capacity, therefore requiring an ONM. On the other hand, ONM is usually perceived as less comfortable than NM and could reduce the compliance [8].

The aim of this study was to assess whether the type of NIV interface affects endurance capacity in COPD patients who were not eligible for home NIV and to describe the incidence, the type and the influence of patient-ventilator asynchronies on endurance capacity according to the interface. The secondary objectives were to evaluate the effects of interface type on perceived exertion, comfort, cardiopulmonary parameters and to assess the ventilator capacity to deliver sufficient support using breathing pattern, flow and pressure tracing analysis as an indirect surrogate for ventilator performance. It was hypothesized that, due to the mode of breathing during exercise (i.e., predominantly oral), high levels of leaks and patient-ventilator asynchrony would occur with nasal masks and would compromise exercise endurance.

2. Experimental Section

2.1. Study Design and Participants

This prospective, randomized cross-over trial was approved by the French ethics committee Nord-Ouest I (CPP-SC 010/2015). It was prospectively registered at https://clinicaltrials.gov (NCT02796599) and is reported according to the CONSORT statement.

All consecutive patients with clinically stable (one month) severe to very severe COPD and a ventilatory limitation during exercise referred for PR at Aide à Domicile pour les Insuffisants Respiratoires (ADIR) Association, Rouen University Hospital, France, were screened for eligibility

between June 2016 and February 2018. They were not included if they were eligible for long-term NIV [3]. Details about inclusion, non-inclusion and exclusion criteria are available in Appendix A. Written informed consent was obtained from all patients.

2.2. Clinical and Functional Evaluation

As part of their baseline assessment which took place within the two weeks before attending the PR program, all patients underwent a complete evaluation including pulmonary function tests and evaluation of exercise capacity using the six-minute walk test and CPET on the same day. Subsequently, patients were offered to participate in the study. Details about the procedures are available in Appendix B.

2.3. Protocol

Those patients who accepted to participate in the study took part in three visits. These visits were separated by a minimum of 48 h and took place within a maximum of two weeks. The experimental procedure was successfully respected for each of the participants.

Visit 1: First, patients were allowed 15 to 20 min to become accustomed to the NIV (Trilogy, Respironics Inc., Murrysville, PA, USA) at rest with both NM and ONM (Eson TM and Simplus TM, Fisher & Paykel Healthcare, Auckland, New-Zealand) in a sitting position. NIV was delivered with a single limb circuit and both masks were provided with intentional leaks port. NIV settings at rest were positive expiratory pressure (PEP) 4 cmH2O, pressure support 5 cmH2O.

Secondly, patients performed a constant workload exercise testing (CWET) on spontaneous breathing (SB) which was used as an anchor of perceived exertion for the subsequent titration of the NIV parameters.

Third, after a 15-min resting period, another exercise session was carried out at the same workload intensity as the CWET in SB in order to determine the appropriate NIV settings for visits two and three. Patients were asked to breathe through the nose as long as possible when using NM. Based on previous studies suggesting that higher pressure would provide more benefits in exercise capacity, dyspnea and respiratory work of breathing [19–22], and that the addition of a PEP could further improve these benefits (counterbalancing for the intrinsic PEP) [22,23], the aim of the titration was to reach both the highest pressure support and PEP tolerated. Both interfaces were tested according to the randomization and the following protocol was used: first, progressive rise in pressure support (2 cmH2O/minute) and secondly PEP (1 cmH2O/min; using the pressure support level previously chosen) as long as the patient felt more comfortable compared with the first CWET during SB or until it became uncomfortable. The highest pressure support and PEP tolerated were used for the subsequent evaluations. Thirdly, pressure rise time was also adjusted according to the patient's tolerance. "Auto-Trak" mode was used for the inspiratory and expiratory trigger.

Visits two and three: Patients performed a CWET under NIV with NM or ONM (randomized order) using the settings determined during visit one.

CWET: CWET were performed according to current guidelines [24]. After a one-minute warm-up period (unloaded), patients were asked to maintain a load corresponding to 75% of Wmax at 70 revolutions per minute (rpm) until exhaustion. No encouragement was given except the time every minute. The test ended when patients stopped because of symptoms or when the cycling speed dropped by 10 rpm for more than 10 s.

2.4. Randomization

The randomization was carried out using a computer-generated sequence (www.randomized.org). After completion of the first CWET with SB, the order of the two subsequent tests (with NM or ONM) was randomized by an individual unrelated to the study (concealed allocation).

2.5. Outcomes

The primary outcome was maximal endurance time (Tlim) of the CWET between the three conditions (SB, NM and ONM).

Secondary outcomes: a comprehensive analysis of the flow and pressure raw data from the ventilator were used to assess patient-ventilator asynchrony, breathing pattern, and were used as a surrogate for ventilator performance. Further methodological details are provided in Appendix C.

Interface comfort: mask comfort was assessed after both NIV tests using a visual analogue scale (VAS), ranging from 0 (extremely uncomfortable) to 10 (extremely comfortable).

Perceived exertion: dyspnea and lower limb fatigue were both assessed at rest and every 30 s using the Borg scale [25].

Transcutaneous oxygen and carbon-dioxide measurement: transcutaneous oxygen saturation (SpO2) and transcutaneous carbon-dioxide partial pressure (TcPCO2) were continuously recorded using a capnograph (SenTec, ResMed, San Diego, CA, USA) at the earlobe. It was set up at least 20 min before each CWET to allow calibration of the signal. In order to assess SpO2 and TcPCO2 signals at a similar time point, TcPCO2 was analyzed with a 2 min lag-time [26].

2.6. Statistical Analysis

A sample size calculation was carried out to detect a clinical positive effect of NIV using an ONM compared with NIV using a NM on endurance exercise capacity during a constant CWET (assessed as Tlim (s)). Accordingly, 15 patients were required to detect a minimal clinical important difference of 101 s (SD 100 s) in Tlim [27] with a 95% power at the 0.05 significance level. We planned to recruit 21 patients to account for attrition due to intolerance of NIV in people not eligible to and to further improve the power of the study (99% power in the situation where all patients would complete the study).

Normality of the distribution of each variable was assessed using a Shapiro–Wilk test. Categorical data were expressed as counts (%) and continuous data were expressed as means (SD or 95% CI) or medians (25th–75th percentiles) depending on the distribution.

Cardiorespiratory outcomes were analyzed both at iso time and at Tlim. Iso time was defined as the Tlim of the shortest CWET. Comparisons between interfaces were performed using a paired t-test or a Wilcoxon Signed Rank test. Multiple comparisons were performed using paired repeated measures of analysis of variance (ANOVA) or Friedman tests. In the case of a significant difference, Wilcoxon tests were performed to explore pairwise comparisons and a Bonferroni correction was applied. Relationships were assessed using Pearson or Spearman correlation tests. Patients with an increase in Tlim for more than 101 s or 33% with any interface compared with the SB test were deemed as improvers [27] and were considered for further analysis in order to assess whether baseline characteristics might predict responsiveness to NIV using an independent t-test or a Mann-Whitney test according to the data distribution.

In order to assess changes in respiratory parameters and ventilator performance, a comparison was made between the cycle by cycle mean of the 60 first and the 60 last seconds of CWET. Patients with less than two minutes of records were excluded for this analysis (four with ONM and six with NM. Moreover, the variation of each indicator between the beginning and the end of exercise was calculated as follows: Indicatorvar = Indicatorend − Indicatorbeg.

Comparison in the proportion patient with AI > 10% between interfaces was performed using the Fisher test.

3. Results

3.1. Patients

One hundred fifty-four patients were screened for eligibility and twenty-one were included in the study. There were no dropouts (Figure 1).

Patients characteristics are shown in Table 1. Nine (43%) were female and five (24%) were long term oxygen users. All had severe obstruction (mean FEV1%: 35.3% (±8.3)), were severely hyperinflated (mean RV/TLC: 0.6 (±0.1) and had impaired exercise capacity (mean VO2peak: 12.1 mL/kg/min (±2.8).

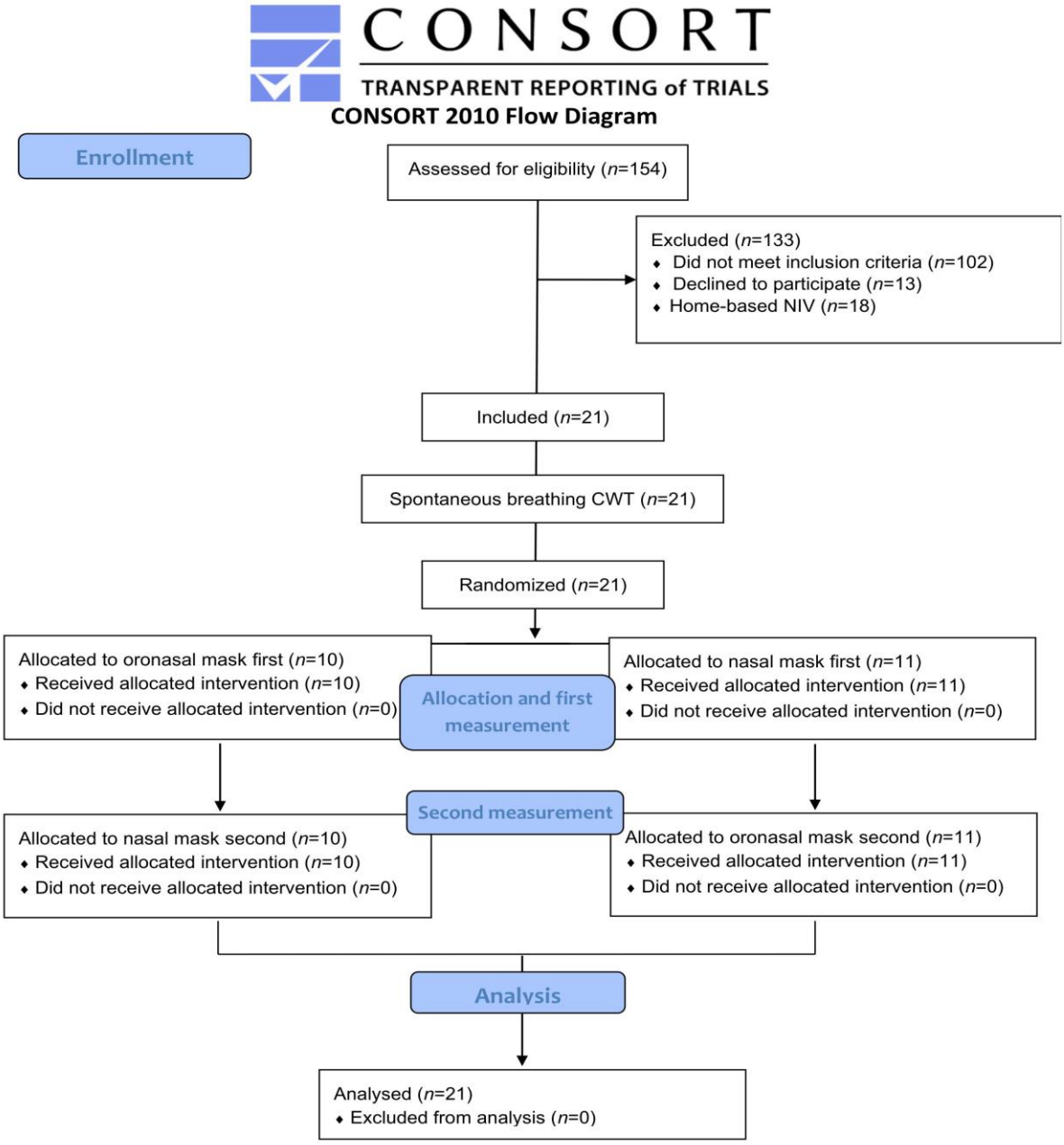

Figure 1. Flow-chart. NIV: noninvasive ventilation; CWET: constant workload exercise testing.

Table 1. Characteristics of the participants.

Variable, (Units)	Participants (n = 21)
Female (n)	9 (43) [a]
Age (years)	58.9(10.7) [b]
Height (cm)	170 (8.9) [b]
Body mass (kg)	66.1 (11.9) [b]
BMI (kg/m^2)	22.8 (3) [b]
FEV1 (L)	0.9 (0.8–1.3) [c]
FEV1 (%)	35.3 (8.3) [b]
FVC (L)	2.6 (0.8) [b]
FEV1/FVC (% ratio)	40.2 (8.8) [b]
RV (L)	4.5 (0.9) [b]
RV (%)	216 (43) [b]
TLC (L)	7.4 (1.3) [b]
RV/TLC	0.6 (0.1) [b]
IC (L)	1.7 (0.6) [b]
IC (%)	65 (17) [b]
VO2 peak (mL/kg/min)	12.1 (2.8) [b]
Arterial blood gas	50 (40–70) [c]
PaO2 (mmHg)	67.5 (12) [b]
PaCO2 (mmHg)	38.3 (4.5) [b]
pH	7.44 (0) [b]
HCO3- (mmol/L)	24.8 (23–25) [c]
Wmax (W)	50 (40–70) [c]
6MWT (m)	413.5 (99.1) [b]
LTO (n)	5 (24) [a]
BODE	4.3 (1.7) [b]

[a] Values expressed as numbers (%); [b] Values expressed as means (SD); [c] Values expressed as medians (25th–75th percentile). FEV1/FVC is expressed as a percentage ratio. BMI: body mass index; FEV1: forced expiratory volume in one second; FCV: forced vital capacity; RV: residual volume; TLC: total lung capacity; IC: inspiratory capacity; VO2peak: maximal oxygen consumption; PaO2: oxygen arterial partial pressure; PaCO2: carbon dioxide arterial partial pressure; HCO3-: bicarbonates; Wmax: maximal workload achieved during cardiopulmonary exercise testing; 6MWT: six-minute walk test; LTO: long-term oxygen; BODE: Body mass index, airflow Obstructive, Dyspnea, and Exercise capacity index.

NIV Parameters: See Table S1.

3.2. Primary Outcome

There were no order effects between tests (p = 0.84). There was a significant difference in Tlim between SB, ONM and NM due to the significant reduction in this variable with both masks (respectively 406 s (IQR 197–666), 240 s (IQR 131–385) and 189 s (IQR 115–545), $p < 0.01$). However, there was no significant difference between interfaces (p = 0.34) (Figure 2).

Three patients (14%) were considered as improvers and eighteen (86%) as non-improvers. Only inspiratory capacity (IC%) was significantly higher in improvers (81% (SD 1) versus 62% (SD 17), $p < 0.01$). There was no significant difference in the proportion of improvers among patients whose TcPCO2 increased for more than 4 mmHg during the SB test compared with those whose TcPCO2 did not increase.

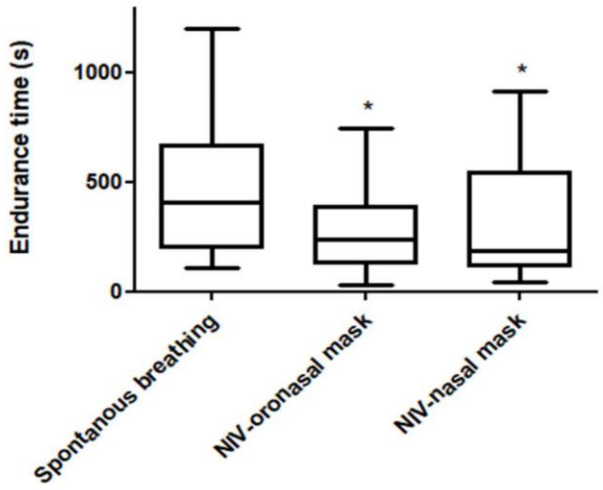

Figure 2. Endurance time for each condition. NIV: noninvasive ventilation. *: significantly lower than the spontaneous breathing condition, $p < 0.02$ (Friedman one-way analysis of variance and Wilcoxon post hoc analysis).

3.3. Secondary Outcomes

3.3.1. Patient-Ventilator Asynchrony

Data from 42 exercise sessions with NIV (for a total of 13,415 s and 5136 respiratory cycles) were analyzed. Total asynchrony index (AI) (%) according to the interface is shown in Table 2.

Table 2. Asynchrony index according to the interface.

Event (%)	Interface		Between-Group Comparison
	Oronasal Mask ($n = 21$)	Nasal Mask ($n = 21$)	p
Normal cycles	95.5 (91.6–97.0)	82.5 (47.1–95.5)	$p < 0.01$
Ineffective triggerings	0 (0–0.1)	2.1 (0–21.5)	$p < 0.01$
Double-triggerings	0.2 (0–1.6)	2.7 (0.7–8.6)	$p < 0.01$
Auto-triggerings	1.7 (0–3.6)	1.7 (0.4–2.5)	NS
Premature cyclings	0.2 (0.0–1.9)	0.9 (0.0–6.9)	NS
Delayed cyclings	0.0 (0.0–0.8)	0.0 (0.0–2.3)	NS
NDP	96.6 (94.8–98.3)	87.2 (68.4–96.8)	$p < 0.01$
Total major asynchrony events	3.4 (1.7–5.2)	12.8 (3.2–31.6)	$p < 0.01$

Values are expressed as medians (25th–75th percentile). NDP: sum of normal cycle, premature and delayed cycling. Total major asynchrony events are the sum of ineffective efforts, double-triggering and auto-triggering. NS, not significant.

The proportion of patients with AI > 10% for ineffective efforts (IE) was significantly higher with NM than with ONM (33.3 versus 0%, $p < 0.01$). The difference was not significant regarding double-triggering (DT) (19 versus 0%, $p > 0.1$) or auto-triggering (AT) (5 versus 0%, $p = 1$). During tests with NM, endurance time was significantly higher in subjects with more than 10% IE AI (592.9 s (SD 385.3)) compared with those with 10% or less (258.9 s (SD 134.3)), $p < 0.05$).

The median total major AI (%) significantly increased only for NM from the beginning (5% (IQR 0–13.6) to the end of exercise (15% (IQR 3.6–45), $p = 0.04$) mainly due to a significant increase in IE (from 0% (IQR 0–4.6) to 2.9% (IQR 0–30), $p < 0.05$) (Figure S1).

There was no significant relation between NPD, total major asynchronies AI% and both endurance time or interface comfort for the two interfaces.

3.3.2. Flow and Pressure Tracing Analysis

Comparison in flow and pressure measurement between the beginning and the end of exercise and between interfaces are shown in Table S2.

Comparison of flow and pressure between subjects with IE AI ≤ 10% or > 10% for NM are shown in Table S3.

3.3.3. Cardiopulmonary Outcomes

Compared with SB, SpO2 increased with both ONM and NM (respectively 95.2% (SD 1.6), 97.1% (SD 1.1) and 97% (SD 1.2), $p < 0.05$) at rest. Conversely, TcPCO2 was significantly reduced with the ONM compared with SB (36 mmHg (SD 3) and 38 mmHg (SD 3.6) respectively, $p < 0.05$). Vt, unintentional leaks and RR were not significantly different at rest between interfaces while they significantly differed during exercise. Table 3.

Table 3. Effects of non-invasive ventilation on cardiopulmonary outcome at iso-time and time limit.

Variables, (Units)	Constant Workload Exercise Testing			Between-Group Comparison
	Spontaneous Breathing (n = 21)	Oronasal Mask (n = 21)	Nasal Mask (n = 21)	p
Iso-time				
Heart rate (bpm)	111.6 (17)	118.2 (13.4)*	116.5 (11.1)	$p < 0.05$
SpO2 (%)	93.1 (3)	93.5 (2.4)	93.4 (2.4)	NS
TcPCO2 (mmHg)	39.1 (4.4)	40.2 (3.2)	39.9 (3.9)	NS
Respiratory rate (cpm)		27.6 (6.7)	24.7 (8.6)	NS
Vt (mL)		1333.6 (486.2)	784.3 (486.2)	$p < 0.01$
Unintentional leaks (L/min)		12.2 (9.6)	28.3 (29.8)	$p < 0.03$
Time limit				
Heart rate (bpm)	121.1 (15.3)	120.5 (13.7)	120 (13.7)	NS
SpO2 (%)	92.8 (3.2)	93.1 (2.6)	93.1 (2.9)	NS
TcPCO2 (mmHg)	38.5 (4.5)	39.5 (2.9)	40 (4)	NS
Respiratory rate (cpm)		30.3 (5.4)	24.9 (9.6)	$p < 0.01$
Vt (mL)		1225.6 (494.2)	828.3 (506.2)	$p < 0.01$
Unintentional leaks (L/min)		11.7 (9.6)	28.9 (31.3)	$p < 0.04$

Values expressed as means (SD). *: significantly higher than spontaneous breathing, $p < 0.04$. Respiratory rate, Vt and unintentional leaks were recorded by the built-in software of the ventilator. bpm: beats per minute; SpO2: transcutaneous oxygen saturation; TcPCO2: transcutaneous carbon-dioxide partial pressure; cpm: cycles per minute; Vt: volume tidal; NS: not significant. NS, not significant.

Other respiratory parameters are shown in Table S4.

3.3.4. Interface Comfort

There was no significant difference in comfort between the ONM and NM (respectively, 4.95 (SD 2.5) and 4.86 (SD 2.6), $p = 0.88$).

3.3.5. Perceived Exertion

There were no significant differences between the three tests for dyspnea or lower limb fatigue at iso time and for dyspnea at Tlim. Compared with SB, lower limb fatigue was significantly reduced with both ONM and NM (respectively 6.3 (SD 2.9), 4.8 (SD 3.2) and 5.1 (SD 3.1), $p < 0.05$).

3.3.6. Relationship between Outcomes

There was no significant relation between NPD, total major AI% and both endurance time and interface comfort for the two interfaces. Additionally, there was a positive significant relationship between IE AI% and endurance time with NM (r = 0.47, $p = 0.03$).

4. Discussion

The results of this study show that NIV during exercise did not improve endurance exercise capacity with any type of interfaces (an may even worsened exercise capacity), without any significant

differences between them. Patient-ventilator asynchrony was relatively infrequent with ONM but significantly increased with NM (median AI: 12.8%). Particularly, IE AI% was clinically relevant for 33% of the patients with NM and was positively correlated with endurance time (r = 0.47, $p = 0.03$). The comprehensive flow and pressure tracing analysis revealed that the ventilator likely reached its performance limits, particularly with NM.

Because of its complexity and the many parameters influencing its use, NIV during exercise is a much-debated topic with divergent results, particularly when used over a course of PR. Indeed, previous acute and physiological studies has mostly demonstrated a significant positive effect of NIV on exercise capacity [11,12,28–30] or no positive effects [31,32], while long-term studies remain inconclusive [7,18,33]. In this context, the detrimental effect of NIV on endurance exercise capacity found in the present study was quite unexpected and it is therefore difficult to differentiate between a real worsening in endurance exercise capacity or a lack of improvement (there is also a possibility of a type 1 statistical error). Conservatively, other factors also contribute to explain the lack of improvement observed with NIV.

First, we found that those patients with a lower IC% at rest were more likely to be not-improvers. This is in line with (i) Oliveira et al., who found that NIV adversely affects "central" hemodynamics adjustments to exercise and was associated with a lack of improvement in exercise capacity in patients severely hyperinflated at rest and (ii) O'Donnell et al. who had previously shown that the inability to further expand Vt during exercise was an important factor contributing to exercise limitation in hyperinflated COPD patients [34]. Because our participants were further hyperinflated than those who participated in the study of Oliveira et al. and much more than those involved in previous studies which found positive effects of NIV [11,30], it is likely that they could not further expand their Vt even with NIV due to their hyperinflation even though they experienced the central hemodynamics side effects of NIV. On the other hand, subjects with a lower extent of hyperinflation who are still able to expand their Vt may still benefit from NIV [12].

Additionally, other factors such as the low pressure support used [3,4], NIV-induced hypercapnia [31,35] or the patient's selection (i.e., without chronic hypercapnic respiratory failure (CHRF)) may also explain the lack of improvement in Tlim. Indeed, higher inspiratory support may have led to a positive effect of NIV as suggested by Gloeckl et al. who found a significant improvement in endurance capacity with high-pressure NIV during exercise in patients already undergoing long-term NIV for CHRF [36]. Although some other studies suggest the use of the highest tolerable inspiratory support [37], the median support was only 8 cmH2O in the present study and higher levels were not tolerated by these patients who were naive to NIV. However, it was within the ranges of those used in studies that found that NIV improved endurance capacity [19,20] and matched with the level of pressure support titrated to comfort used in Anekwe et al. [13]. Based on the available evidence, we included patients with severe obstruction and ventilatory limitation [7,8,38] and did not include those patients who were eligible to home NIV to prevent bias relating to experience. However, although the NIV was initiated at rest and then titrated during exercise, in laboratory conditions and by a physiotherapist experienced in NIV, it is possible that the patients were insufficiently acclimatized to the NIV. Moreover, these negative results in patients not eligible for long-term NIV supports two recent studies performed specifically in patients with CHRF patients [29,38]. Altogether, these results suggest that, during exercise, NIV may be particularly effective in patients who are already under home NIV and tolerate higher pressure support (i.e., CHRF).

Beyond the selection of the patients and the pressure support used, our results support other mechanisms to explain the decreased endurance performance with NIV, which differ between interfaces.

4.1. Oronasal Interface

There were few patient-ventilator asynchronies with ONM (median total AI < 4%) and their occurrence was not related with endurance time, so they were likely to be clinically irrelevant. Conversely, flow measurements significantly increased throughout exercise and were superior to those

with NM. Particularly, Fini progressively rose up with ONM (+24 L/min compared with +3 L/min with NM, $p < 0.01$). Theoretically, it is not supposed to increase during exercise if the ventilator sufficiently assists the patient, suggesting a lack of power of the ventilator. Moreover, Fmax, mean and Fmax, end reached about 200 L/min (which is the maximal flow generating capacity of the ventilator used according to the manufacturer), while Pinspi significantly decreased all along the exercise suggesting that the ventilator was unable to maintain the set pressure despite the fact the maximal flow generating capacity was reached. In addition, the pressure rise time (τ) was set to the fastest setting available on the ventilator (i.e., "1", corresponding to a duration of 100 ms to reach the set pressure from the beginning of the inspiratory cycle according to the manufacturer data). However, τini and the mean τ for both interfaces were largely superior this value (400 ms), suggesting that the ventilator was unable to rise the pressure as quickly as set, again suggesting a technological limitation.

These observations extend those from a previous study which also found markers of technological limitation during exercise in COPD patients, even though an intensive care unit ventilator was used [13]. This supports the idea that the ventilator was not able to maintain even the low pressure support used in the present study (although low, Pinspi decreased all along the exercise while the maximal flow generating capacity of the ventilator was reached), therefore it is unlikely that a higher pressure support could have been reached. Therefore, although potentially contributing, the low inspiratory support used was not the primary explanation for the lack of improvement in the endurance exercise capacity observed in the present study because higher pressure would have been limited by technological limitations.

4.2. Nasal Interface

The reason for the altered performance with NM is more complex. IE was the most frequent, clinically relevant patient-ventilator asynchrony (33% of the patients reached the clinical level of significance of 10% [39]) and was significantly related with endurance performance. Although the positive nature of this relation is primarily surprising, it can be explained by several factors. First, those patients with more than 10% IE AI had significantly more leaks and a negative value of Fini, var. This strongly suggests that these patients began to exercise breathing through the nose and then by the mouth when exercise became more difficult (Figure S1) in such a way that these patients breathed "over" the ventilator, eliciting IE and lower Vt and RR recorded by the ventilator at time limit (IE cycle values not recorded (Table 3)).

This is strengthened by the fact that AI% significantly increased with NM from the beginning to the end of exercise and that those patients with a high level of asynchrony had a significantly higher Tlim, as in the spontaneous breathing test.

On the other hand, two thirds of the patients did not open the mouth and had a similar pattern to ONM (i.e., less asynchronies but a decreased endurance capacity). Contrary to ONM, the Fmax, end (about 180 L/min) was below the maximal generating capacity of the ventilator and the set pressure support was reached, suggesting that it could have been further increased. This observation raises concern about the possibility to adjust NIV parameters throughout the exercise. This difference with ONM likely lies in the higher resistance of the upper airway which helped to reach the set pressure with a lower flow. However, higher support was not tolerated by the patients and the relatively low margin for the flow to increase (about 20/min) makes the possibility to further expand it difficult to achieve without reaching the technological limitation of the ventilator. Moreover, some markers of the technological limitations of the ventilator were already present (pressure rise time set not reached). Altogether, these results suggest that the important amount of IE observed in a third of the patients (who breathed through the mouth at the end of exercise) was a consequence either of a direct technological limitation or an insufficient support that could not have been further expanded due to technological limitation.

4.3. Implication for Practice and Research

The main strength of this study is that it was conducted in a condition close to that which would be used if NIV was used to sustain higher training intensity during PR (75% Wmax). Our negative results do not exclude a positive effect of NIV at a lower relative intensity [29], where the inspiratory flow is lower and may not exceed the ventilator generating capacity. Accordingly, NIV should be used as a "starter" to initiate PR and more rapidly reach the prescribed length of training (generally 30–45 min [14,40,41]) rather than a "booster" to sustain higher training intensity as suggested by physiological studies [9,42,43]. Moreover, this study supports the use of ventilator displaying Fmax value on the monitoring screen to help clinicians to assesses whether the ventilator is powerful enough to relieve respiratory effort for a given exercise. Finally, our results suggest that the respiratory support needed by the patients, as well as patient-ventilator asynchronies, varies throughout the exercise. Therefore, the effects of automated modes that could adapt more easily to the different exertions of exercise (such as those using a volume-assured pressure support and automated PEP) deserve to be studied.

4.4. Limits of the Study

First, neither the patients nor the assessor were blinded. However, it is unlikely to influence patient-ventilator asynchronies or the technological capacity of the ventilator. Secondly, the SB condition was carried out first, and was not randomized. This choice was made to allow a perceived exertion anchor for the subsequent NIV parameters titration because most of the patients with COPD are not used to exercise. Moreover, it helped to avoid any possible ordering effect relating to the procedure between masks. Lastly, flow pressure tracing and respiratory parameters were derived from the raw data of the built-in software of the ventilator respectively and not from an external pneumotachograph and pressure transducer, which may have introduced some errors in the measurements due to leaks [44,45] and precluded any comparison between the SB tests with both masks.

5. Conclusions

In patients with COPD not acclimated to long-term home mechanical ventilation, during-exercise NIV delivered through either NM or ONM does not improve endurance capacity (and may even worsen it). Patient-ventilator asynchrony was uncommon with ONM and endurance performance was likely impaired due to technological limitation of the ventilator. Patient-ventilator asynchrony, particularly IE, was more frequent with NM and reflects the fact that some patients shunted the ventilator by breathing through the mouth. This likely occurred either because of an insufficient pressure support (with few possibilities to increase it due to technological limitations) or directly due to a technological limitation of the ventilator.

Supplementary Materials: The following are available online at http://www.mdpi.com/2077-0383/9/4/1054/s1, Figure S1: Comparison in ventilatory dynamic between the beginning (**A**) and the end (**B**) of exercise in a representative subject with nasal mask. Table S1: Noninvasive ventilation settings. Table S2: Comparison in flow and pressure between the beginning and the end of exercise. Table S3: Comparison of flow and pressure between subjects with IE AI $\leq$ 10% or > 10% for nasal interface. Table S4: Comparison of cycle time, instantaneous respiratory rate and Ti/Ttot between interfaces.

Author Contributions: Conceptualization, T.B., F.-E.G., C.M., G.P., Y.C., J.-F.M., A.C., D.D., G.R., M.P. and C.V.; Data curation, F.-E.G.; Formal analysis, T.B., E.F. and A.K.; Investigation, T.B. and F.-E.G.; Methodology, T.B., F.-E.G., C.M., G.P., Y.C., J.-F.M., A.C., D.D., G.R., M.P. and C.V.; Project administration, J.-F.M., A.C., M.P. and C.V.; Supervision, D.D. and C.V.; Validation, T.B. and C.V.; Writing—original draft, T.B.; Writing—review & editing, T.B., F.-E.G., E.F., A.K., C.M., G.P., Y.C., J.-F.M., A.C., D.D., G.R., M.P. and C.V. All authors have read and agreed to the published version of the manuscript.

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Appendix A

Inclusion: non-inclusion and exclusion criteria.
Inclusion criteria:

- Stable (on month) severe to very severe COPD referred for pulmonary rehabilitation. The clinical diagnosis of COPD was based on a ratio between forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) < 0.70;
- Age ≥ 18 years;
- FEV1 < 50% predicted;
- Ventilatory limitation (breathing reserve < 30%) during the initial cardiopulmonary exercise testing [7,38].

Non-inclusion criteria:

- Eligible to home noninvasive ventilation according to [3]:
- PaCO2 ≥ 51.9 mmHg and pH > 7.35 at rest;
- Potential pregnancy;
- Under guardianship;
- Refusal to consent.

Exclusion criteria:

- Acute exacerbation of COPD (according to the Anthonisen's criteria [46]) before completion of the study.

Appendix B

Clinical and functional evaluation.

Pulmonary function: Pulmonary function tests were performed according to the American Thoracic Society (ATS) and the European Respiratory Society (ERS) guidelines with plethysmography (Masterscreen, Jaeger, Wittsburg, Germany). Values were expressed as a percentage of established theoretical values for European population [47].

Six-minute walk test: The six-minute walk test was carried-out according to the ATS and ERS guidelines in a 30-m corridor [48,49]. The test was performed twice and the best distance was used for analysis.

Cardiopulmonary exercise testing: Cardiopulmonary exercise testing was performed on an electromagnetic braked cycloergometer (Ergoselect 200, Ergoline, Bitz, Germany). Following a 3-min warm-up period, incremental ramp exercise was applied up to exhaustion (5–20 W/min). A pneumotachograph and gas analyzer (Ergocard, Medisoft, Louvain, Belgium) were used to measure gases (oxygen consumption and carbon dioxide production breath by breath) through a face mask (Hans Rudolph, Inc., Kansas City, MO, USA). The last ramp maintained before stopping the exercise was used to determine the maximal workload (Wmax).

Appendix C

Secondary outcomes.

A comprehensive analysis of the flow and pressure raw data from the ventilator were used to assess patient-ventilator asynchrony, breathing pattern, and were used as a surrogate for ventilator performance.

Patient-ventilator asynchrony: According to the framework proposed by the SomnoNIV group, the following asynchrony events were assessed [50–53]:

Rate asynchronies: rate asynchronies are defined as a mismatch between ventilator and patients' rates [53] and include:

- Ineffective effort (IE): IE is characterized by an inspiratory effort not assisted by the ventilator. It can be identified as a drop of airway pressure associated with increase or decrease of airflow (if occurring during expiratory or inspiratory phase respectively) [52];
- Double-triggering (DT): DT is characterized by two mechanical cycles triggered by the patient, separated by a very short expiratory time (< 30% of mean inspiratory time) [52];
- Auto-triggering (AT): AT is characterized by the presence of mechanical cycle unrelated to patient's spontaneous breathing [52];

Intracycle asynchronies: intracycle asynchronies were defined as a distortion of the flow and pressure curves during inspiration and/or expiration [53] and include:

- Premature cycling (PC): PC reflects a situation where the end of the mechanical insufflation anticipates patient's own inspiration termination [52];
- Delayed cycling (DC): Otherwise to PC, DC is a condition where the mechanical insufflation exceeds the patient's own neural expiration [52].

Quantification of asynchronies: Rate asynchronies (IE, DT and AT) were considered as major asynchrony event [52]. PC and DC were considered as minor event. Cycles corresponding to none of these categories were considered as normal. Normal cycles, PC and DC were pooled and termed as NPD.

Each major asynchrony event and total major asynchronies were standardized using the previously described asynchrony index (AI(%)) dividing the asynchronous breath by the sum of ventilator cycles and IE, expressed as percentage [39,50,51]. An AI > 10% was considered as clinically relevant [39,50,51].

Breathing pattern, flow and pressure tracing analysis: Respiratory rate (RR), tidal volume (Vt) and unintentional leaks were recorded by the built-in software of the ventilator. As the ventilator recorded total leakage, unintentional leaks were estimated at each time point by subtracting the intentional leak for each mask at a given pressure level (manufacturer's data) from total leak. For every patient with both interfaces and for every NPD cycle, the following data were collected: cycle time, instantaneous respiratory rate (IRR; calculated as the inverse of cycle time), pressure rise time (τ), Ti/Ttot ratio, flow at the beginning of the cycle (Fini), maximal flow (Fmax), minimal pressure (Pmin), maximal pressure (Pmax) and mean inspiratory pressure (Pinspi; from the beginning of the cycle to the transition to minimal pressure).

Moreover, several indicators were calculated from cycle by cycle analysis as follow:

- Mean differential flow (Fdiff) = Fmax, mean − Fini, mean;
- Mean differential pressure (Pdiff) = Pmax, mean − Pmin, mean.

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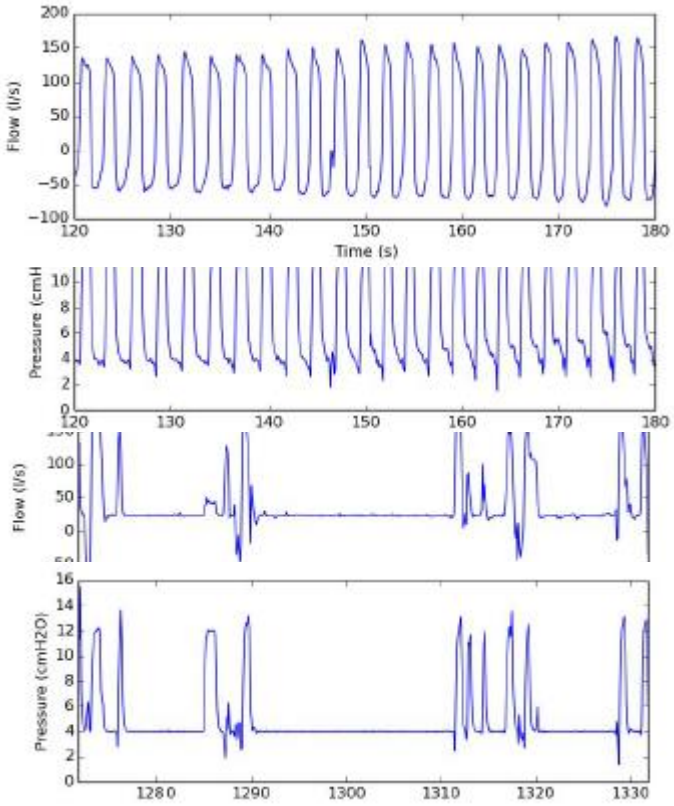

Figure S1: Comparison in ventilatory dynamic between the beginning (A) and the end (B) of exercise in a representative subject with nasal mask. The occurrence of ineffective effort at the end of exercise is in coherence with mouth leaks.

Table S1: Noninvasive ventilation settings.

Variables (units)	Interface		Between-group comparison *p*
	Oronasal mask (n = 21)	Nasal mask (n = 21)	
Inspiratory support (cmH2O)	8 (8-10)	10 (8-10)	NS
Expiratory positive airway pressure (cmH2O)	4 (4-5)	4 (4-5)	NS
Slope	1 (1-3)	1 (1-2)	NS

Values expressed as medians (25th-75th percentile).

Table S2: Comparison in flow and pressure between the beginning and the end of exercise.

Variable, (units)	**Moment during exercise**		**Intra-group comparison**
	First minute	Last minute	*p*
Fini (L/min)			
Oronasal interface, n=17	33.2 (26.2-39.4)[b]	75.9 (44.6-109.2)[b]	**p<0.01**
Nasal interface, n=15	41.5 (22.2-49.0)[b]	38.0 (30.8-58.7)[b]	NS
Between-group comparison, *p*	NS	**p<0.05**	
Fmax (L/min)			
Oronasal interface, n=17	149.2 (124.7-174.7)[b]	214.0 (200.2-230.2)[b]	**p<0.01**
Nasal interface, n=15	128.1 (99.9-148.6)[b]	132.1 (110.5-179.0)[b]	**p<0.01**
Between-group comparison, *p*	**p<0.05**	**p<0.01**	
Pinspi (cmH2O)			
Oronasal interface, n=17	10.0 (9.3-11.8)[b]	8.7 (8.5-10.5)[b]	**p<0.01**
Nasal interface, n=15	10.3 (2.8)[a]	10.3 (2.4)[a]	NS
Between-group comparison, *p*	NS	NS	
Pmax (cmH2O)			
Oronasal interface, n=17	13.9 (2.0)[a]	14.7 (2.1)[a]	**p<0.01**
Nasal interface, n=15	13.7 (3.1)[a]	14.3 (3.2)[a]	**p<0.05**
Between-group comparison, *p*	NS	NS	
Pmin (cmH2O)			
Oronasal interface, n=17	4.3 (0.6)[a]	3.3 (0.7)[a]	**p<0.01**
Nasal interface, n=15	4.1 (0.6)[a]	3.8 (0.5)[a]	**p<0.05**
Between-group comparison, *p*	**NS**	**p<0.05**	
Pdiff (cmH2O)			
Oronasal interface, n=17	9.6 (2.1)[a]	11.4 (2.2)[a]	**p<0.01**
Nasal interface, n=15	9.6 (2.8)[a]	10.5 (2.9)[a]	**p<0.01**
Between-group comparison, *p*	NS	NS	

[a]Values expressed as means (SD). [b]Values expressed as medians (25th-75th percentile). Fini: flow at the beginning of the cycle; Fmax: maximal flow; Pinspi: mean inspiratory pressure; Pmax: maximal pressure; Pmin: minimal pressure; Pdiff: differential pressure.

Table S3: Comparison of flow and pressure between subjects with IE AI ≤ 10% or > 10% for nasal interface.

Variables (units)	Proportion of ineffective effort asynchrony index (%)		Between-group comparison
	≤ 10% (n = 8)	> 10% (n = 7)	*p*
$P_{inspi,beg}$ (cmH2O)	11.3 (9.7-14.4)	8.6 (8.2-9.2)	**p<0.05**
$P_{inspi,end}$ (cmH2O)	10.3 (8.0-13.3)	9.1 (8.9-10.0)	NS
$P_{min,var}$ (cmH2O)	-0.47 (-0.6 - -0.28)	0.00 (-0.12-0.01)	**p<0.05**
IRR_{var}	7.4 (5.5-13.0)	3.4 (-1.8-5.3)	NS
Leaks (L/min)	8.2 (4.5-14.4)	25.6 (10.8-32.1)	**p<0.05**
$F_{ini,beg}$ (L/min)	22.2 (19.3-23.2)	48.9 (46.2-51.8)	**p<0.01**
$F_{ini,var}$ (L/min)	15.0 (9.3-43.3)	-10.5 (-12.9-2.6)	**p<0.01**
$F_{ini,end}$ (L/min)	39.5 (29.3-58.1)	37.7 (32.9-48.9)	NS
$F_{max,beg}$ (L/min)	142.7 (132.2-148.9)	102.8 (91.4-118.5)	NS
$F_{max,end}$ (L/min)	179.0 (171.4-181.2)	110.5 (101.4-126.0)	**p<0.01**
$F_{max,var}$ (L/min)	36.3 (31.5-45.2)	1.9 (-3.6-12.5)	**p<0.05**
$F_{diff,beg}$ (L/min)	112.8 (106.5-126.3)	50.1 (42.9-78.0)	**p<0.01**
$F_{diff,end}$ (L/min)	122.3 (104.8-143.2)	72.8 (61.8-74.8)	**p<0.01**
τ_{beg} (ms)	447.4.8 (438.1-488.8)	425.0 (376.2-461.8)	NS
τ_{end} (ms)	448.2 (403.0-496.3)	432.7 (356.9-513.66)	NS

Values expressed as medians (25th-75th percentile). Pinspi: mean inspiratory pressure; beg: outcome assessed at the beginning of exercise; Pmin: minimal pressure; var: difference between the end minus the beginning of exercise; IRR: instantaneous respiratory rate; Fini,: flow at the beginning of the cycle; end: outcome assessed at the end of exercise; Fmax: maximal flow; Fdiff: differential flow; τ: pressure rise time.

Table S4: Comparison of cycle time, instantaneous respiratory rate and Ti/Ttot between interfaces.

Variables (units)	Interface		Between-group comparison
	Oronasal mask (n = 21)	Nasal mask (n = 21)	*p*
IRR_{mean}	25.5 (4.9)[a]	23.7 (4.6)[a]	**p<0.05**
IRR_{var}	7.1 (5.2)[a]	4.3 $(5.9)_a$	NS
CT_{mean}	2.2 (2.2-2.8)[b]	2.6 (2.3-2.9)[b]	**p<0.05**
$Ti/Ttot_{mean}$ (%)	29.2 $(0.1)_a$	29.3 (0.1)[a]	NS
τ_{mean} (ms)	458.8 (419.5-530.1)[b]	477.1 (448.7-497.7)[b]	NS

[a]Values expressed as mean (SD). [b]Values expressed as medians (25th-75th percentile). IRR: instantaneous respiratory rate; CT: cycle time; Ti/Ttot: ratio between inspiratory time and total time; τ: pressure rise time.

II.4. Utilisation de l'électrostimulation excito-motrice ou antalgique pour optimiser les effets du réentrainement à l'exercice

L'électrostimulation se définit comme la délivrance de stimuli préprogrammés aux nerfs, aux muscles ou aux articulations par l'intermédiaire d'électrodes de surface positionnées sur la peau, dans le but de fournir un effet thérapeutique aigu et/ou chronique (155). Il existe trois types de stimulations électriques décrits ci-après :

- La stimulation électrique fonctionnelle ;
- La stimulation électrique excito-motrice ;
- La stimulation électrique nerveuse transcutanée.

II.4.a. La stimulation électrique fonctionnelle :

Elle consiste en l'application d'un courant électrique cyclique et d'intensité modérée sur des muscles. Elle est principalement utilisée pour générer des mouvements fonctionnels et restaurer des fonctions perdues. Ainsi, ses effets sont principalement retrouvés durant la stimulation (155). Les effets de l'électrostimulation électrique fonctionnelle chez les patients atteints de BPCO a déjà fait l'objet de travaux au sein de notre laboratoire (156, 157).

II.4.b. La stimulation électrique excito-motrice :

Elle consiste en l'application de stimuli électriques (biphasique) intermittents de haute intensité pour susciter des contractions musculaires relativement fortes, le plus souvent dans des conditions tétaniques (fréquence entre 60 et 100Hz). Elle est principalement utilisée pour la rééducation neuromusculaire et musculaire. Ses effets sont principalement obtenus après des séances répétées (155). La contraction musculaire induite par la stimulation électrique diffère de la contraction volontaire dans sa composante temporelle (respectivement synchrone et

asynchrone), spatiale (respectivement fixe, superficielle et dispersée)) et sélective (respectivement non sélective des unités motrices et sélective). Lors de la stimulation électrique excito-motrice, la surface d'activation musculaire dépend de l'intensité de la stimulation (158). Par ailleurs, en deçà d'un niveau minimal d'intensité (définie comme la rhéobase), aucune contraction musculaire ne peut se produire. La contraction musculaire dépend également du temps de stimulation dont la durée optimale définie comme la chronaxie, correspond au temps pendant lequel doit être appliqué une intensité double à celle de la rhéobase pour déclencher le potentiel d'action (159). Enfin, le placement des électrodes est un autre élément majeur garant de l'efficacité de la stimulation. La détection et l'application individualisée du courant sur les points moteurs musculaires (lieu de la jonction neuro-musculaire) permet un meilleur recrutement musculaire et un meilleur confort pour le patient (160, 161).

En pratique clinique, l'intérêt de l'électrostimulation excito-motrice pour les patients atteints de BPCO réside dans le fait qu'elle offre la possibilité d'une stimulation musculaire aussi efficace que celle obtenue lors d'une contraction musculaire volontaire mais à un coût cardiorespiratoire et métabolique inférieur (62, 124, 162, 163). Ainsi, son utilisation s'est largement répandue dans les services de réanimation ou chez les patients atteints de BPCO présentant un handicap ventilatoire trop important pour participer à un programme de réhabilitation (121-123, 164). Cependant, son intérêt en tant qu'adjuvant à la réhabilitation respiratoire a été peu étudié et les conclusions des études réalisées sont limitées pour des raisons méthodologiques (165-167).

Étude n°7

Effets de la stimulation électrique excito-motrice comme complément à la réhabilitation respiratoire – Étude randomisée contrôlée multicentrique

Home-based Neuromuscular Electrical Stimulation as an Add-on to Pulmonary Rehabilitation Does Not Provide Further Benefits in Patients With Chronic Obstructive Pulmonary Disease: A Multicenter Randomized Trial

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ORIGINAL RESEARCH

Home-based Neuromuscular Electrical Stimulation as an Add-on to Pulmonary Rehabilitation Does Not Provide Further Benefits in Patients With Chronic Obstructive Pulmonary Disease: A Multicenter Randomized Trial

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Abstract

Objective: To assess the additional effect of a home-based neuromuscular electrical stimulation (NMES) program as an add-on to pulmonary rehabilitation (PR), on functional capacity in subjects with chronic obstructive pulmonary disease (COPD).

Design: Single-blind, multicenter randomized trial.

Setting: Three PR centers.

Participants: Subjects with severe to very severe COPD (N=73; median forced expiratory volume in 1 second, 1L (25th–75th percentile, 0.8–1.4L) referred for PR. Twenty-two subjects discontinued the study, but only 1 dropout was related to the intervention (leg discomfort).

Intervention: Subjects were randomly assigned to either PR plus quadricipital home-based NMES (35Hz, 30min, 5 time per week) or PR without NMES for 8 weeks.

Main Outcome Measure: The 6-minute walk test (6MWT) was used to assess functional capacity.

Results: Eighty-two percent of the scheduled NMES sessions were performed. In the whole sample, there were significant increases in the distance walked during the 6MWT ($P<.01$), peak oxygen consumption ($P=.02$), maximal workload ($P<.01$), modified Medical Research Council dyspnea scale ($P<.01$), and Saint George's Respiratory Questionnaire total score ($P=.01$). There was no significant difference in the magnitude of change for any outcome between groups.

Conclusions: Home-based NMES as an add-on to PR did not result in further improvements in subjects with severe to very severe COPD; moreover, it may have been a burden for some patients.

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Chronic obstructive pulmonary disease (COPD) will be 1 of the 3 principal causes of mortality worldwide in 2020.[1] This respiratory disease progressively impairs ventilation, leading to exertional dyspnea.[2] Moreover, the disease has systemic effects, including

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lower limb muscle atrophy, which further reduces physical capacity.[3,4] This reduction in physical capacity is associated with poor outcomes and a poor prognosis.[4,5] However, pulmonary rehabilitation (PR), self-management, and education programs have been shown to be effective in reversing the systemic effects.[6,7]

Neuromuscular electrical stimulation (NMES) is an adjunct treatment used to reduce muscle wasting and improve muscle function.[8-10] In patients with COPD, NMES is commonly applied to the quadriceps muscle since quadriceps dysfunction is strongly associated with both loss of functional capacity and morbidity, independent of respiratory function.[4] It is widely used in patients with COPD in the intensive care unit or during hospitalization for acute exacerbations, because the associated metabolic energy cost is low.[11-13] In this situation, NMES has been shown to effectively reduce muscle wasting and dyspnea and increase functional capacity in patients with COPD.[12,14]

Recently, NMES has been proposed as a home treatment for patients with COPD.[10,15] Maddocks et al[10] showed that a 6-week, supervised, home-based NMES program improved exercise capacity in patients with COPD who were unable to participate in comprehensive PR. The results showed increases in 6-minute walk test (6MWT) distance, maximal voluntary contraction of the quadriceps, and in the cross-sectional area of the rectus femoris with NMES. However, there was no effect on daily physical activity or quality of life (QoL), in contrast with PR.

Most of the studies have assessed NMES as an alternative for patients who could not attend PR, and few have evaluated its use as an add-on to a comprehensive PR program. Moreover, the few studies[16-18] are generally limited by poor methodology.

The objective of this study was to assess the effect of a home-based NMES program as an add-on to PR, on functional capacity in patients with COPD. We hypothesized that a home-based NMES program in addition to PR could enhance the benefits of PR.

Methods

Study design and participants

This prospective, multicenter, randomized controlled trial was approved by the French ethics committee Nord-Ouest I. This study was registered at https://clinicaltrials.gov (NCT02171377).

Consecutive individuals with stable COPD referred to 3 PR centers in Normandy were screened for eligibility between August 2010 and December 2013. Inclusion criteria were (1) aged ≥18 years; (2) forced expiratory volume in 1 second <60% predicted with a total lung capacity >80% predicted; (3) baseline modified Medical Research Council dyspnea scale ≥1; (4) motivated to participate in PR; and (5) optimized medical therapy. Exclusion criteria were (1) body mass index (BMI) <18 or >35kg/m^2; (2) pregnancy or potential pregnancy; (3) peripheral neuropathy; (4) contraindication to cardiopulmonary exercise testing (CPET); (5) progressive cancer; (6) cardiac pacemaker; (7) implanted cardiodefibrillator; and (8) refusal to consent. Written informed consent was obtained from all subjects.

List of abbreviations:

BMI	**body mass index**
COPD	**chronic obstructive pulmonary disease**
CPET	**cardiopulmonary exercise testing**
NMES	**neuromuscular electrical stimulation**
PR	**pulmonary rehabilitation**
QoL	**quality of life**
SGRQ	**Saint George's Respiratory Questionnaire**
6MWT	**6-minute walk test**
$\dot{V}O_2$	**oxygen consumption**
V_{O_2}**peak**	**peak oxygen consumption**

Randomization

After completion of their baseline assessment, subjects were randomly assigned to receive either PR plus NMES (PR+NMES group) or PR alone (PR group) by an individual unrelated to the study (concealed allocation). The randomization was generated by blocks of 6 subjects by a statistician using a computer-generated sequence. Randomization was stratified by center and centralized so that investigators were not involved in the procedure.

Clinical and functional evaluation

All subjects underwent a complete evaluation before and after the intervention, including pulmonary function tests,[19] evaluation of exercise capacity using the 6MWT (the test was carried out twice with a 1-h rest between tests, and the longest distance was used in the analysis)[20] and CPET,[21] and health-related QoL using the St George's Respiratory Questionnaire (SGRQ; a lower score indicates a better QoL).[22] Dyspnea was assessed using the modified Medical Research Council scale.[23] The BMI, airflow obstruction, dyspnea, and exercise capacity index were noted.[24] The number of subjects using long-term oxygen in each group was recorded at baseline.

Cardiopulmonary exercise testing

CPET was performed on an electromagnetic ergometer (Ergoselect 200[a]). After a 3-minute warmup period, incremental ramp exercise (5−20W/min) was applied up to exhaustion. A face mask,[b] pneumotach, and gas analyzer (Ergocard[c]) were used to measure gases (oxygen consumption [$\dot{V}O_2$] and carbon dioxide production [$\dot{V}CO_2$]) breath by breath. The ventilatory threshold was manually determined as the average of 4 methods: (1) first break of the ventilation; (2) increase in the minute ventilation ($\dot{V}E$)/$\dot{V}O_2$ ratio without modification of the $\dot{V}E/\dot{V}CO_2$ ratio (Wasserman's method); (3) raise in the expired carbonic gas; and (4) Beaver's method.[21,25] Heart rate was continuously monitored with a 12-lead electrocardiogram.

Intervention

Pulmonary rehabilitation

All subjects participated in a comprehensive PR program (outpatient or home-based) including respiratory physiotherapy, and strength and endurance training on a cycloergometer, 3 to 5 times per week, for 8 weeks. After an initial 5 minute warmup period, subjects performed 20 to 35 minutes of a steady-state training at the intensity recorded at the ventilatory threshold during baseline CPET. Training was followed by a 5-minute cooldown period. Intensity was then incremented during the following training sessions based on perceived exertion (dyspnea or muscular fatigue assessed using the Borg scale[26]) as previously described.[27] The PR program also included muscle strength

training (3 sets of 12 movements at 70% of maximal resistance or using resistive bands) for 30 minutes. Strength training mainly focused on the lower limbs but also included upper limb strengthening. In the case of home-based PR, a cycloergometer was made available at home for endurance training, and an initiation session was performed at home by a trained physiotherapist. Strength training and respiratory physiotherapy were performed with a community-based physiotherapist. Patients were contacted by phone every 2 weeks by a physiotherapist from the PR center to follow and adapt training. Educational, nutritional, and psychological support were offered as needed (performed in the centers for every subjects).

Home-based NMES

In addition to PR, the PR+NMES group underwent bilateral NMES of the quadriceps muscle (Mi-Theta-Pro device[d]) at home. They were instructed to carry out 30 minutes of stimulation, 5 times per week during the 8 weeks of the program. Three self-adhesive surface electrodes were placed on each thigh (one 10×5-cm electrode on the proximal part of the rectus femoris and two 5×5-cm electrodes on the distal parts of the vastus medialis and the vastus lateralis). The device delivered a biphasic symmetric current with a pulse duration of 400 milliseconds. After a 2-minute continuous warmup at 6Hz, the intensity was individually adjusted to just under the pain threshold. The stimulation then alternated between contractions and active rest phases for 25 minutes. The frequencies used were 35Hz for the contractions and 4Hz for the active rest phases, with a duty cycle of 0.5 and 1.5 seconds, respectively. The session was completed with a 3-minute recovery period at 3Hz. Each subject in the PR+NMES group was taught to use the device by a trained physiotherapist. The NMES was then carried out autonomously at home, and subjects were told to increase the intensity as tolerated. Thereafter, the physiotherapist was available by telephone should the subject have any questions related to its use, but no formal feedback to the therapist or contact from the therapist was scheduled.

Outcomes

The primary outcome was change in functional capacity evaluated by the difference in distance walked during the 6MWT between the pre- and postevaluations.

Secondary outcomes were peak oxygen consumption (Vo_2peak [mL/kg/min]), maximal workload during CPET, dyspnea measured by the modified Medical Research Council scale, the BMI, airflow obstruction, dyspnea, and exercise capacity index, and health-related QoL, including SGRQ subscores (symptom, activity, and impact) and a total score.

Statistical analysis

Normality of the distribution of each variable was assessed using the Shapiro-Wilk test. Categorical data were expressed as counts (%), and continuous data were expressed as means (SD or 95% confidence interval) or medians (25th−75th percentile) depending on the distribution. Within-group comparisons were performed using a paired t test or a Wilcoxon rank test, and between-groups comparisons were carried out using an independent t test or a Mann-Whitney test, depending on the distribution. A P value $<.05$ was considered statistically significant. By considering a minimal clinically important difference of 35m between groups on the 6MWT[28] and an SD of 44m,[29] the actual power of the study was above 76% for a .05 significance level.

Prism 5 software[e] was used for all analyses.

Results

Patients

Seventy-four patients were screened for eligibility, and 73 were randomly assigned to either PR (n=36) or PR+NMES (n=37). Twenty-two patients dropped out during the study with no significant difference in the dropout rate between groups (25% for PR group vs 35% for PR+NMES group, $P=.45$) (fig 1).

The demographic data of the 51 patients included in the study are shown in table 1. Briefly, 7 (14%) were women, 14 (28%) were long-term oxygen users, mean age ± SD was 59.2±9.6 years, median (25th−75th percentile) BMI was 23.5kg/m^2 (20.2−27kg/m^2), and median (25th−75th percentile) forced expiratory volume in 1 second was 1L (0.8−1.4L). Baseline characteristics were similar between groups before the intervention except for Vo_2peak, which was significantly lower in the PR+NMES group ($P=.05$).

Intervention

Twelve patients (23.5%) performed the PR at home. There was no difference in the number of sessions performed between the PR and PR+NMES groups (median no. of sessions, 24 (18−25) and 24 (21.3−26.8), respectively; $P=.27$). The median duration of each session was 31 minutes (30−35.5min) for the PR group and 35±8.1 minutes for the PR+NMES group ($P=.16$). Patients in the PR+NMES group performed a mean ± SD of 32.9±12.7 sessions of electrical stimulation (ie, 82% of the prescribed sessions) at a median (25th−75th percentile) intensity of 65mA (41.5−87mA). One patient discontinued the stimulation because of discomfort. No other adverse events were recorded during the study.

Effectiveness of PR program

One patient did not undergo CPET and 5 did not complete the SGRQ at the end of the intervention because of technical problems. In the whole sample, after rehabilitation, the distance walked during the 6MWT increased ($P<.01$), as did Vo_2peak ($P=.02$), maximal workload during CPET ($P<.01$), modified Medical Research Council ($P<.01$), and SGRQ total score and impact subscore ($P=.01$ and $P=.02$, respectively) (table 2).

Primary outcome

In the PR group, the distance walked on the 6MWT increased (from 452±80.3m to 473±83.9m, $P=.02$); however, the post-training distance was not significantly different between groups, and there were no differences in the magnitude of change between groups (fig 2, table 3).

Secondary outcomes

Peak Vo_2

The Vo_2peak improved significantly in the PR group after rehabilitation ($P=.04$), but not in the PR+NMES group ($P=.22$).

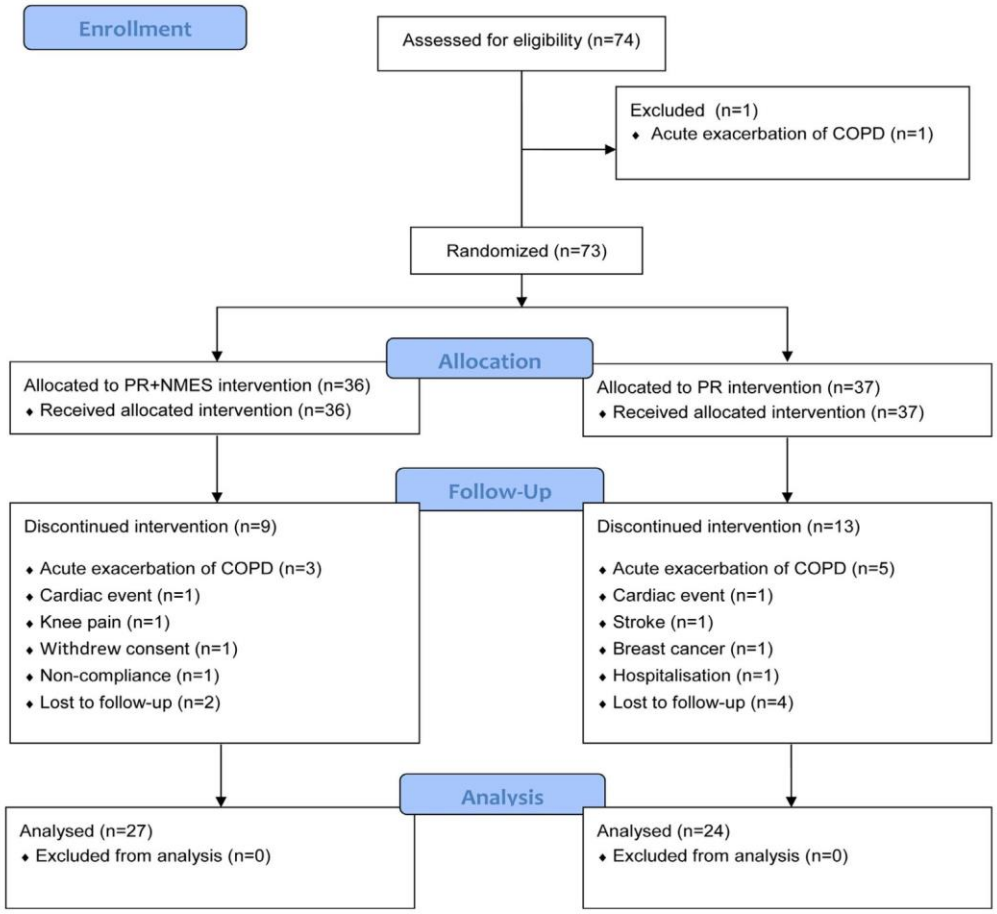

Fig 1 Flow chart.

There was a significant difference in Vo_2peak between groups after rehabilitation (14.7±2.5 mL/kg/min for the PR+NMES group vs 15.8ml/kg/min (15−18.6) mL/kg/min for the PR, $P=.02$). However, the magnitude of change was not different between groups (see table 3).

Saint George's Respiratory Questionnaire

The SGRQ total score and impact subscore only improved in the PR group (both $P=.03$). There were no significant differences between the posttraining values of each group or the magnitude of change between groups (fig 3, see table 3).

There were no significant changes in any group for the SGRQ symptoms and activity subscores. The SGRQ symptoms subscore was significantly lower in the PR group compared with the PR+NMES group after intervention (29.7±17.1% vs 20.4±13.2%, respectively; $P=.05$), but there was no difference in the magnitude of change between groups (see fig 3 and table 3).

Discussion

The results of this study showed that PR improved functional capacity, Vo_2peak, dyspnea, and QoL in patients with COPD. To our knowledge, this study is the first to assess the effects of a home-based NMES program in addition to PR. However, the NMES did not provide further benefits to PR, as there were no significant differences in the magnitude of change between groups for any outcome. The postintervention symptom subscore of the SGRQ was significantly higher in the PR+NMES group, suggesting a negative effect of NMES on that aspect of QoL.

The improvement in performance on the 6MWT (+19.3m) in the whole sample was slightly less than the recently suggested minimal clinically important difference (+25m)[30]; however, the improvements in maximal workload during CPET (+6.6W) and QoL (−4.4%) were both greater than the minimal clinically important difference (+4W[30] and −4%, respectively).[22] Since QoL is an important patient-centered outcome, this shows that the PR program improved patient health status.

The effects of NMES in patients with COPD are inconsistent across studies. Two recent meta-analyses[31,32] stated that NMES improved quadriceps muscle strength and exercise capacity. However, the effects of NMES in addition to a comprehensive PR program have only been assessed in 3 randomized studies.[16-18] Kucio et al[17] found a significant improvement in functional capacity after PR plus NMES, but there was no direct comparison between groups. Zanotti et al[18] also found a significant improvement in 6MWT performance after PR with the addition of NMES compared with sham NMES. The results of the present study are in accordance with the study by Tasdemir et al[16] that showed no further benefits when NMES was added to a comprehensive PR program. Moreover, the improvement in functional capacity was significantly smaller with the addition of

Table 1 Patient characteristics

Variable	PR+NMES (n=27)	PR (n=24)	*P*	Total Population (N=51)
Women	2 (7)	5 (19)	.23	7 (14)
Age (y)	61.2±10.2	57±8.6	.12	59.2±9.6
Height (cm)	169.2±5.8	170±9	.70	169.6±7.4
Body mass (kg)	70 (60–79)	65 (54.5–78.3)	.30	68 (57–79)
BMI (kg/m^2)	24.5 (20.6–28.1)	21.6 (19.9–25.9)	.18	23.5 (20.2–27)
FEV1 (L)	1 (0.8–1.3)	1.1±0.3	.34	1 (0.8–1.4)
FEV1 (%)	34.6 (28.3–38.5)	37±8.3	.33	35 (30–40.3)
FVC (L)	2.5 (2.1–2.9)	2.9±0.7	.27	2.7±0.8
FEV1/FVC (% ratio)	42.2±9.5	40±7.4	.37	41.2±8.5
RV (L)	5.2±1.3	5±1.1	.62	5.1±1.2
TLC (L)	8.1±1.5	8.3±1.4	.64	8.2±1.4
COPD stage				
GOLD I				0 (0)
GOLD II	3 (11)	2 (8)	>.99	5 (10)
GOLD III	13 (48)	13 (54)	.78	26 (51)
GOLD IV	11 (41)	9 (38)	>.99	20 (39)
V_{O_2}peak (mL/kg/min)	14.2±2.1	16 (13.5–17.6)	.05	14.8 (13.1–16.5)
Wmax (W)	59.3±16.2	68.8±19.4	.10	60 (50–70)
6MWT (m)	425 (375–500)	452.1±80.3	.43	450 (385–495)
SGRQ				
Symptoms (%)	32.4±20	31.6±21	.87	32±20.3
Activity (%)	72.2±11.3	67.2±18.8	.64	73 (60.5–79)
Impact (%)	40±16.4	33.5 (18.5–40.3)	.12	37 (25–44.5)
Total (%)	47 (38–55)	43.6±15.5	.22	46.3±13.9
LTO (n)	6 (22)	8 (33)	.53	14 (28)
BODE	4 (3–5)	3.5 (3–4.8)	.18	4 (3–5)
mMRC scale	2 (2–3)	2 (1.3–2)	.06	2 (2–2)

NOTE. Values are n (%), mean ± SD, median (25th–75th percentile), or as otherwise indicated.
Abbreviations: BODE, BMI, Airflow Obstructiion, Dyspnea, and Exercise Capacity Index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LTO, long-term oxygen; mMRC, modified Medical Research Council; RV, residual volume; TLC, total lung capacity; Wmax, maximal workload achieved during CPET.

NMES.[16] The lack of benefit of NMES in Tasdemir's study[16] could be attributed to the low frequency of use (twice a week); however, this is unlikely since the present study found similar results with stimulation 5 days per week. Although unsupervised, the number of sessions performed in the present study (30 sessions, ie, 82% of the prescribed sessions) and the final intensity (median, 65mA) were both within the ranges of those used in studies[9,10,14,18] that found improvements after NMES in patients with COPD. We therefore do not believe that the discrepancies between the results of these studies are related to the regimens or modalities used. The explanation may lie in the patient characteristics and rehabilitation regimen.

First, the sample studied by Zanotti[18] had mild COPD, while in the study by Tasdemir[16] and in the present study, the patients had severe to very severe COPD. The muscle dysfunction that occurs in COPD has been shown to be at least partially reversible.

Table 2 Effectiveness of PR program (N=51)

Outcome	Pre	Post	Mean Difference [95% CI]	*P*
6MWT (m)	450 (385–495)	462 (400–520)	19.3 [8.2 to 30.4]	<.01
V_{O_2}peak (mL/kg/min)	14.8 (13.1–16.5)	15.4 (13.5–17.8)	0.7 [0.1 to 1.3]	.02
Wmax (W)	60 (50–70)	67.5 (58.8–80)	6.6 [3.6 to 9.6]	<.01
mMRC scale	2 (2–2)	2 (1–2)	−0.3 [−0.5 to −0.1]	<.01
BODE	4 (3–5)	4 (3–5)	−0.1 [−0.4 to 0.2]	.58
SGRQ				
Symptoms (%)	32±20.3	25.6±16	−3 [−7 to 1]	.21
Activity (%)	73 (60.5–79)	66 (60–79.3)	−1.8 [−6.5 to 2.8]	.62
Impact (%)	37 (25–44.5)	31.9±19.4	−5.1 [−9.3 to −0.9]	.02
Total (%)	46.3±13.9	40.9±14.7	−4.4 [−7.8 to −1.1]	.01

NOTE. Values are mean ± SD, median (25th–75th percentile), or as otherwise indicated.
Abbreviations: BODE, BMI, Airflow Obstructiion, Dyspnea, and Exercise Capacity Index; CI, confidence interval; mMRC, modified Medical Research Council; Wmax, maximal workload achieved during CPET.

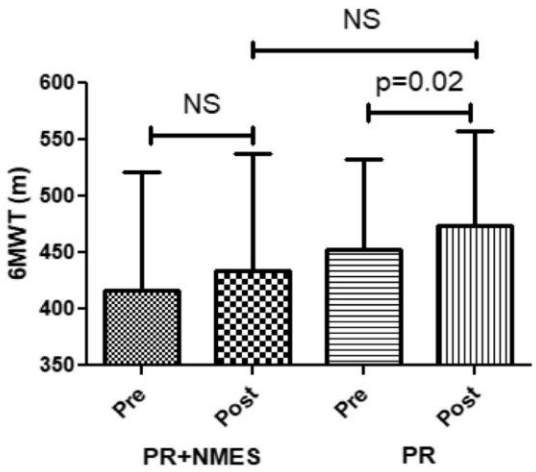

Fig 2 Improvement in 6MWT distance after the interventions. Abbreviation: NS, not significant.

However, the relationship between severity and extent of recovery over time is unknown.[33] It could therefore be hypothesized that patients with severe to very severe COPD might achieve their maximal possible improvement from either NMES alone or PR alone; thus, the combination does not result in further improvement. In contrast, patients with less severe respiratory disease might have a larger capacity for improvement, as suggested by their different response to exercise stimulation,[34,35] and might experience further benefits with additional muscle stimulation (such as NMES). This is supported by the fact that numerous rehabilitation techniques, such as inspiratory muscle training, have been found effective when used alone in patients with COPD.[36,37] However, the additional benefit of adding inspiratory muscle training to PR remains debated.[37,38]

The PR program in Zanotti's study[18] only involved endurance training, which may have been enhanced by NMES since it targets muscle strength. In contrast, the PR programs evaluated by Tasdemir[16] and the present study included both endurance and strength training and were not enhanced by NMES. Sillen et al[9] recently showed that high-frequency NMES improved quadriceps strength and functional capacity as effectively as strength training in patients with COPD and severe disability. Therefore, it could be argued that in patients with severe COPD enrolled in PR, the maximum possible physiological improvement is attained with PR alone. NMES could therefore be a useful addition to endurance training instead of strength training, or when strength training is not possible. However, combining strength training and NMES does not provide more benefits than either modality alone. This hypothesis needs to be confirmed in studies of intrinsic muscle function.[14,36]

At the end of the PR, QoL was improved in the whole sample. Although the extent of change was similar between groups, the symptom subscore of the SGRQ was statistically and clinically higher for the PR+NMES group,[22] suggesting a negative effect of NMES on this aspect of QoL. Home-based NMES 5 times per week might have focused the patients' attention on their disease. Because psychological acceptance of the disease is an important determinant of outcome in patients with COPD,[39] it is not surprising that the addition of a time-constraining treatment, that moreover did not produce further benefits, might have been an added burden for these patients with little spare energy.

The main strength of this study was the clinical implication of the findings, since it was carried out in "real conditions." In order to promote access to PR, patients living far from the centers performed their PR at home (23.5%), providing external validity to this multicenter study because it offered PR in a wide range of models, as occurs in clinical practice. Because home-based PR has been shown to be as effective as center-based PR,[40] it was assumed that this did not interfere with the results. Moreover, since one of the aims of PR is to increase self-management and autonomy,[6] NMES was performed at home with minimal resources (i.e. no supervision). The results suggest that it was feasible (82% of the prescribed sessions were carried out) but ineffective. However, the number of sessions carried out varied greatly across subjects, with some carrying out more than the number prescribed and others much fewer. It is possible that NMES as an add-on to PR may be effective if subjects are accurately selected (based on motivation, feasibility within the home context, etc). This question could be addressed in future studies.

Table 3 Changes after intervention

	PR+NMES		PR		Comparison of Changes Between Groups After Intervention	
Outcome	Mean Difference [95% CI]	*P*	Mean Difference [95% CI]	*P*	Difference Between Means (PR − PR+NNES) [95% CI]	*P*
6MWT (m)	17.5 [1.8 to 33.2]	.54	21.33 [4.6 to 38.1]	.02	−3.9 [−26.3 to 18.6]	.73
V_{O_2}peak (mL/kg/min)	0.5 [−0.3 to 1.3]	.22	1.1 [0.2 to 1.9]	.04	−0.5 [−1.8 to 0.7]	.37
Wmax (W)	5.9 [1.3 to 10.5]	.01	7.4 [3.4 to 11.4]	<.01	−1.5 [−7.6 to 4.6]	.41
mMRC scale	−0.4 [−0.6 to −0.1]	<.01	−0.2 [−0.5 to 0.1]	.27	−0.2 [−0.6 to 0.2]	.38
BODE	−0.3 [−0.8 to 0.1]	.13	0.2 [−0.3 to 0.7]	.42	−0.5 [−1.1 to 0.1]	.07
SGRQ						
Symptoms (%)	−1.7 [−6.6 to 3.2]	.49	−4.7 [−11.8 to 2.5]	.21	3 [−5.1 to 11.1]	.39
Activity (%)	−0.2 [−4.8 to 4.4]	.93	−4.1 [−13.6 to 5.4]	.57	3.9 [−5.5 to 13.3]	.54
Impact (%)	−6.2 [−11.9 to −0.5]	.03	−3.6 [−10.4 to 3.2]	.19	−2.7 [−11.2 to 5.9]	.54
Total (%)	−5 [−9 to −1]	.03	−3.7 [−10.1 to 2.6]	.23	−1.2 [−8.1 to 5.7]	.72

Abbreviations: BODE, BMI, Airflow Obstructiion, Dyspnea, and Exercise Capacity Index; CI, confidence interval; mMRC, modified Medical Research Council; Wmax, maximal workload achieved during CPET.

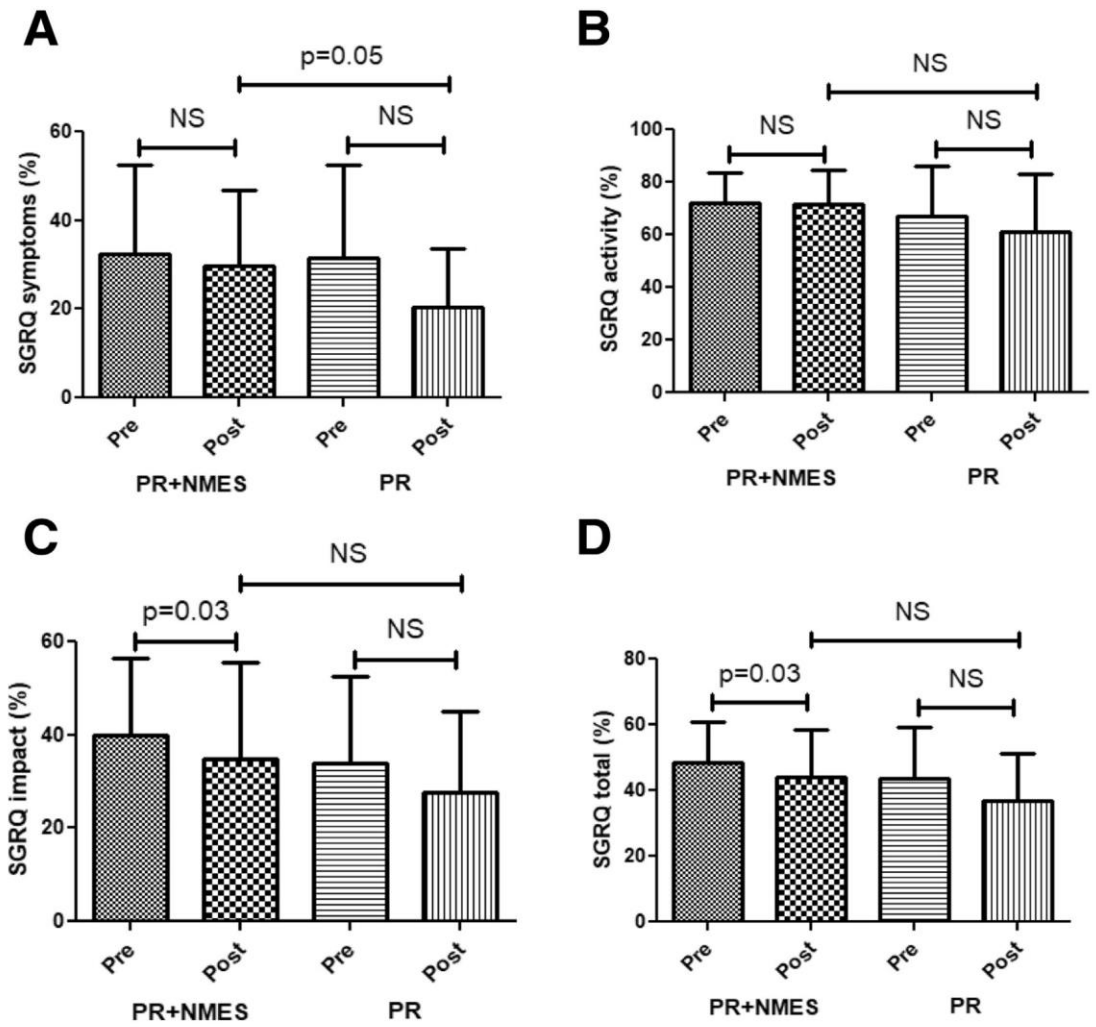

Fig 3 Improvement in SGRQ symptoms subscore (A), activity subscore (B), impact subscore (C), and total score (D) after intervention. Abbreviation: NS, not significant.

Study limitations

This study has some limitations. First, the subjects were not blinded to the treatment allocation. However, because there were no differences between groups, it is assumed that no placebo effect occurred with NMES. Second, the dropout rate was relatively high; however, it was similar to the rates in other studies of PR in real-life conditions.[41,42] Moreover, the dropout rate was similar between groups, and only 1 subject discontinued the NMES as a result of intolerance. Because of the dropouts, the study might have lacked power to detect a difference in the magnitude of changes in the 6MWT between groups. However, the actual power of the study was >76%. Third, there were no outcomes related to muscle strength evaluation, which might have been more sensitive to the NMES intervention than the 6MWT. However, even if an improvement in quadriceps muscle strength occurred with the addition of NMES to PR, the lack of benefits on either functional capacity or QoL would have likely made this result clinically nonrelevant for the subjects. Nevertheless, this outcome as well as the intrinsic muscle function after NMES in addition to PR should be further assessed in a physiological study in order to better understand the underlying mechanisms and the definition of an optimal NMES training regimen. Finally, despite randomization, baseline Vo_2peak was significantly lower in the PR+NMES group, which is the main bias of this study. The effects of NMES might have been confounded because subjects in the PR+NMES group had more severe systemic disease and thus a different response to exercise training.[34,35]

Conclusions

Unsupervised home-based NMES as an add-on to PR does not further improve benefits in subjects with severe to very severe COPD. Moreover, it might be a burden for some subjects. Further sufficiently powered prospective studies are needed to confirm these results. Further studies should also evaluate the effects of NMES and PR on muscle strength and intrinsic muscle structure.

Suppliers

a. Ergoselect 200; Ergoline GmbH.
b. Face mask; Hans Rudolph, Inc.
c. Ergocard; Medisoft.

d. Mi-Theta-Pro device; Compex Medical SA.
e. Prism 5 software; GraphPad Software Inc. Available at: https://www.graphpad.com/.

Keywords

Electrical stimulation; Exercise; Physiotherapy techniques; Pulmonary disease, chronic obstructive; Rehabilitation

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II.4.c. Stimulation électrique nerveuse transcutanée :

Elle consiste en l'application d'un courant électrique continu biphasique de faible intensité aux fibres nerveuses cutanées sans implication musculaire. Elle est utilisée dans le traitement des douleurs aiguë et chronique (168). Il existe deux types de courant antalgique : la stimulation à haute fréquence (80-100 Hz) ou à basse fréquence (2 à 10 Hz). La durée d'impulsion utilisée lors de la stimulation électrique nerveuse transcutanée est relativement courte (≤ 200 µs). Ses effets antalgiques peuvent être retrouvés pendant ou à distance de la stimulation, selon les réglages choisis (155). Les mécanismes physiologiques impliqués dans la diminution de la douleur sont la théorique du *gate control* pour la stimulation électrique nerveuse à haute fréquence (169, 170) ainsi que la libération d'opiacés endogènes (endorphine) pour les stimulations électriques nerveuses à haute ou basse fréquence (via les récepteurs opiacés δ et µ respectivement) (171-173). Bien que l'objectif thérapeutique de l'électrostimulation nerveuse transcutanée soit l'antalgie, son mécanisme d'action physiologique pourrait ouvrir la voie à d'autres applications, notamment l'amélioration de la performance à l'effort des patients atteints d'un handicap ventilatoire. En effet, l'adaptation physiologique à l'exercice est un mécanisme complexe. Il implique trois fonctions étroitement liées : la fonction cardiaque, la fonction pulmonaire et la fonction musculaire. De plus, le niveau d'adaptation cardiorespiratoire pour un effort donné est en partie lié aux muscles réalisant un effort eux-mêmes, par l'intermédiaire des afférences sensorielles musculaires de type III et IV (174, 175) (**Figure 3**). Ces afférences sensorielles sont également impliquées dans l'inhibition musculaire centrale, dont l'objectif est de prévenir une fatigue musculaire potentiellement dangereuse (174-178).

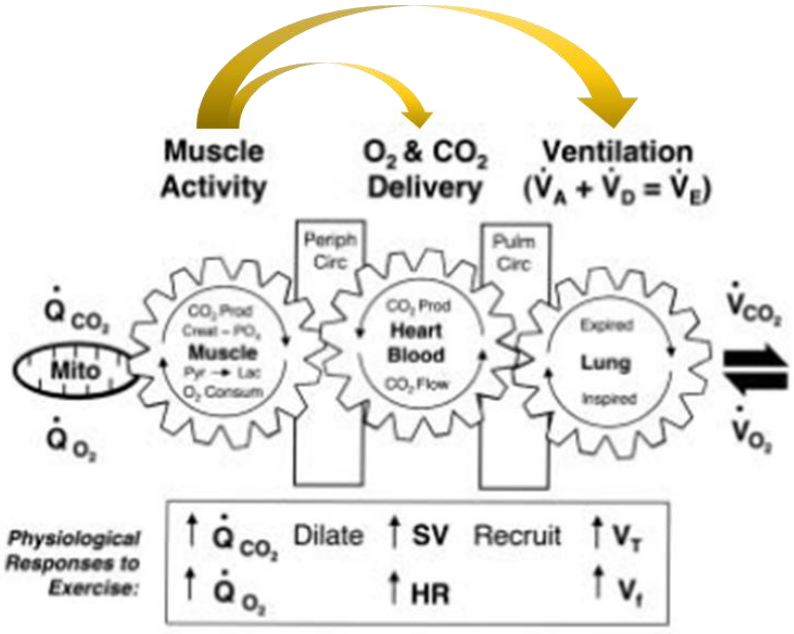

Figure 3 : *Interaction entre les fonctions cardiaque, pulmonaire et musculaire lors d'un exercice. Par l'intermédiaire des afférences sensorielles musculaires de type III et IV, la fonction musculaire contribue à l'adaptation cardiorespiratoire au cours de l'effort, adapté de Wasserman et al. (179).*

Ainsi, chez des athlètes réalisant un exercice à charge constante à haute intensité, chacune des fonctions impliquées dans l'adaptation à l'exercice est sollicitée à un niveau presque maximal. Dans ce contexte, Amman et al. ont montré que l'administration intrathécale de fentanyl (analgésique opioïde), utilisé dans l'objectif de bloquer les afférences musculaires de groupe III et IV pour éviter leurs projections corticales (et ainsi prévenir une inhibition motrice centrale (177)), entrainait une diminution de la réponse cardiorespiratoire à l'effort (dont la ventilation minute et le débit cardiaque) de sorte que, dans cette condition sans aucune autre possibilité de compensation, la capacité à l'exercice était réduite et la fatigue musculaire majorée (174, 175, 178). Cependant, en condition expérimentale durant laquelle l'apport en oxygène aux muscles locomoteurs est maintenu par une supplémentation, l'inhibition centrale et la performance à l'effort sont améliorés (180).

A l'inverse, chez les patients atteints de BPCO, un exercice à charge constante à haute intensité correspond à une intensité absolue nettement inférieure à celle d'athlètes entrainés. Ainsi, la limitation est fréquemment ventilatoire (fonction pulmonaire) (181) mais les autres systèmes conservent des possibilités d'adaptation. Dans ce contexte, Gagnon et al. ont montré que l'administration intrathécale de fentanyl entrainait une réduction de la ventilation minute à l'effort, améliorant ainsi la mécanique respiratoire, l'efficience ventilatoire et la dyspnée (182). De plus, dans cette situation où les autres fonctions ne sont pas sollicitées au niveau maximal, toute altération éventuelle du débit cardiaque en réponse au fentanyl aurait la possibilité d'être compensée par une augmentation de l'extraction musculaire périphérique en oxygène. Au total, les résultats de cette étude montrent que l'inhibition des afférences musculaires de groupe III et IV permet d'améliorer la tolérance à l'effort (temps d'endurance) et d'augmenter la fatigue musculaire périphérique (préalable important pour le développement musculaire (183)) (182).

En pratique courante, l'administration intrathécale de fentanyl semble difficile à effectuer en routine au cours d'un programme de réhabilitation respiratoire mais d'autres stratégies, basées sur les mêmes mécanismes physiologiques, méritent d'être évaluées. Dans la mesure où la stimulation électrique nerveuse transcutanée active les mêmes récepteurs opiacés que le fentanyl via la libération d'endorphine, notamment dans la corne postérieure de la moelle épinière (171, 172), elle pourrait être utilisée pour améliorer la capacité à l'effort des patients atteints de BPCO (180).

Étude n°8

Effets aigus de la stimulation électrique nerveuse transcutanée lombaire sur la performance à l'effort de patients atteints de BPCO – Étude randomisée en cross-over et double aveugle

Lumbar transcutaneous electrical nerve stimulation to improve exercise performance in COPD patients

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Lumbar transcutaneous electrical nerve stimulation to improve exercise performance in COPD patients

To the Editor:

Muscle group III (Aδ fibres) and IV (C fibres) sensory afferents are involved in the cardiorespiratory adaptation to exercise [1, 2]. Their inhibition with intrathecal fentanyl in the dorsal horn of the spinal cord to block their cortical projections decreases high-intensity constant workload endurance performance in healthy athlete subjects because of a blunted cardiorespiratory response to exercise. In this condition with high metabolic demand, any decrease in ventilation or haemodynamics would compromise performance because of a nearly maximal solicitation without any possibility for a compensatory strategy. In contrast, Gagnon *et al.* [3] have published that the use of spinal anaesthesia with fentanyl with the goal of inhibiting muscle group III and IV fibres in chronic obstructive pulmonary disease (COPD) patients improved dyspnoea and endurance capacity. This improvement was due to the blunted ventilatory response to exercise which improved physiological dead space, ventilatory efficiency and in turn, dyspnoea. Moreover, at this relatively lower external workload compared with healthy subjects, cardiac output and peripheral oxygen extraction were not maximal and any mitigation in cardiac output (if any) would be overcome by an increase in peripheral muscle oxygen extraction [3]. High-frequency or low-frequency transcutaneous electrical nerve stimulation (TENS) provide a less invasive alternative which activates opioid receptors, especially those located in the dorsal horn of the spinal cord [1, 4, 5]. This approach deserves to be studied during exercise and over a course of pulmonary rehabilitation in these patients. We performed a randomised double-blind study (clinicaltrials.gov NCT03312322) to assess whether high-frequency or low-frequency lumbar TENS could improve endurance exercise capacity in patients with COPD. Secondary objectives were to assess the influence of lumbar TENS on perceived exertion, ventilatory pattern and muscle oxygenation. We hypothesised that endurance capacity would be improved with lumbar TENS due to a blunted response in exercise ventilation, which would contribute to improve ventilatory efficacy and reduce exercise dyspnoea. Conversely, we hypothesised that any mitigation in cardiac output (if any) would be compensated by an increase in peripheral muscular oxygen extraction.

Consecutive subjects with severe stable COPD referred for pulmonary rehabilitation were screened for eligibility between October 2017 and October 2018. Inclusion criteria were patients aged ⩾18 years and naive to TENS. Non-inclusion criteria were contraindication to TENS, opiate treatment during the previous 3 months and pregnancy. 25 patients were screened; 12 did not meet the inclusion criteria, two declined to participate, one had recently used opiate treatment and 10 agreed to participate (and provided signed consent; approved by the French ethics committee Est III (number 17.05.15)), which was the sample size chosen to gather preliminary data. Included patients performed three constant workload exercise testing (CWET; 75% of the maximal workload achieved during a previously performed incremental cardiopulmonary exercise testing (CPET)) up to exhaustion, with ⩾24-h rest period between tests, with either high-frequency (100 Hz, 100 µs), low-frequency (4 Hz, 100 µs) or sham (100 Hz, 100 µs, intermittent placebo [6]) TENS in a randomised order (computer-generated sequence and concealed allocation). TENS was set at rest, 10 min prior to each CWET, and maintained throughout the test. The current was biphasic, symmetric and applied through four self-adhesive surface electrodes (5×5 cm) positioned by pair at the L3–L4 level, 2 cm lateral to the lower border of the corresponding vertebrae.

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Lumbar transcutaneous electrical nerve stimulation aimed to block muscle group III–IV sensory afferents does not improve endurance exercise capacity in patients with COPD http://bit.ly/2lZr6Mt

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TABLE 1 Impact of lumbar transcutaneous electrical nerve stimulation (TENS) on endurance exercise capacity and physiological parameters measured at isotime and time limit

	TENS settings			Between-group comparison p-value
	Sham	High frequency	Low frequency	
Subjects	10	10	10	
Endurance time s	280±131	244±108	296±118	0.25
Patient 1	377[#]	380	474	
Patient 2	122[#]	182	207	
Patient 3	124[#]	154	248	
Patient 4	147[#]	148	198	
Patient 5	250	143	104[#]	
Patient 6	442	427	367[#]	
Patient 7	278[#]	342	348	
Patient 8	341	302	271[#]	
Patient 9	225	162[#]	274	
Patient 10	491	202[#]	466	
Isotime				
Dyspnoea Borg	5±2	6±2	5±2	0.59
Lower limb fatigue Borg	5±2	6±1	5±1	0.55
Heart rate beats·min^{-1}	112±25	106±31	118±25	0.32
Respiratory rate beats·min^{-1}	28±8	30±8	29±7	0.38
Tidal volume mL	1132±231	1078±296	1095±270	0.59
V'_E L·min^{-1}	31±10	32±9	32±11	0.67
S_{pO_2} %	89±4	88±3	89±4	0.90
V'_{O_2} mL·min^{-1}	858±318	880±302	883±318	0.72
V'_{CO_2} mL·min^{-1}	787±324	795±315	805±328	0.86
Respiratory exchange ratio	0.9±0	0.9±0.1	0.9±0.1	0.36
V'_E/V'_{O_2}	31 (26–39)	31 (27–39)	30 (26–36)	0.69
V'_E/V'_{CO_2}	37±10	37±8	36±8	0.83
HbO_2 % change from baseline	−140±140	−51±67	−31±38[¶]	**0.02**
HHb % change from baseline	39 (−43–130)	22 (7–228)	65 (−59–211)	0.96
THb % change from baseline	−44 (−198–77)	−24 (−31–33)	41 (−24–59)	0.30
St_{O_2} % change from baseline	−5±3	−3±2	−1±7	0.36
Time limit				
Dyspnoea Borg	7±2	7±1	7±2	0.83
Lower limb fatigue Borg	6±1	6±1	6±1	0.80
Heart rate beats·min^{-1}	118±26	108±31	116±26	0.32
Systolic arterial pressure mmHg	164±27	156±24	149±29	0.14
Diastolic arterial pressure mmHg	79 (72–92)	78 (70–100)	80 (75–92)	0.71
Respiratory rate beats·min^{-1}	30±8	31±7	31±8	0.67
Tidal volume mL	1116±302	1067±262	1149±299	0.51
V'_E L·min^{-1}	32±9	32±8	35±10[¶]	**0.03**
S_{pO_2} %	87±5	88±4	88±4	0.66
V'_{O_2} mLmin^{-1}	899±309	896±265	970±338	0.09
V'_{CO_2} mL·min^{-1}	829±312	808±271	901±345[+]	**0.04**
Respiratory exchange ratio	0.9±0	0.9±0	0.9±0	0.14
V'_E/V'_{O_2}	32±7	32±7	33±9	0.98
V'_E/V'_{CO_2}	36±8	36±8	36±9	0.85
HbO_2 % change from baseline	−109±116	−36±73	−38±34	0.06
HHb % change from baseline	135 (−43–186)	24 (−32–477)	41 (−69–266)	0.62
THb % change from baseline	−44 (−125–79)	−24 (27–50)	−19 (−40–127)	0.30
St_{O_2} % change from baseline	−7±6	−2±4	0±6	0.09

Data are presented as n, mean±SD or median (interquartile range), unless otherwise stated. Repeated measures of ANOVA or Friedman test according to the distribution. V'_E: minute ventilation; S_{pO_2}: oxygen saturation measured by pulse oximetry; V'_{O_2}: oxygen consumption; V'_{CO_2}: carbon dioxide production; HbO_2: oxyhaemoglobin and oxymyoglobin; HHb: deoxyhaemoglobin and deoxymyoglobin; THb: total haemoglobin and myoglobin; St_{O_2}: muscle tissue oxygen saturation. [#]: time limit of the shortest constant workload exercise testing used to define isotime for the subsequent analysis; [¶]: Tukey's *post hoc* comparison, significantly higher than sham TENS, $p<0.05$; [+]: Tukey's *post hoc* comparison, significantly higher than high-frequency TENS, $p<0.05$.

The intensity was adjusted just under the pain threshold every 3 min (and no longer increased during the CWET). Patients were told that they may no longer feel the current during the procedure due to accommodation (or the intermittent nature of the sham TENS), but were asked not to discuss their bodily sensations in order to maintain study blinding. Perceived exertion (dyspnoea and lower limb fatigue assessed every 30 s using the Borg scale), gas exchange and ventilatory patterns (including oxygen consumption and carbon dioxide production, recorded breath by breath (Vyntus CPX; Care Fusion, San Diego, CA, USA) and muscle oxygenation (vastus lateralis muscle relative change in total haemoglobin and myoglobin (THb), oxyhaemoglobin and oxymyoglobin (HbO_2) and deoxyhaemoglobin and deoxymyoglobin), continuously recorded at a frequency of 1 Hz using a near-infrared spectroscopy device (NIRS; PortaMon; Artinis, Einsteinweg, the Netherlands) and tissue oxygen saturation (S_{tO_2}), calculated as the ratio of HbO_2/THb×100 and expressed as change from baseline were monitored during the tests. Statistical analysis was performed using Prism 5 software (GraphPad, San Diego, CA, USA) and comparison between tests was performed using either repeated ANOVA and Tukey *post hoc* tests or Friedman and Wilcoxon *post hoc* tests for pairwise comparison according to the distribution. Secondary outcomes were analysed both at time limit (t_{lim}) and at isotime. Isotime was defined as the t_{lim} of the shortest CWET.

Patients were aged 64 (interquartile range (IQR) 57–67) years, had severe bronchial obstruction (mean±SD forced expiratory volume in 1 s 0.9±0.3 L), significant thoracic distension and decreased exercise capacity (median oxygen uptake 12.3 (IQR 11.2–18.7) $mL \cdot kg^{-1} \cdot min^{-1}$). They all had a ventilatory limitation during the initial CPET. There was no significant difference in endurance capacity between low-frequency, high-frequency and sham TENS nor in dyspnoea or lower limb fatigue at isotime or t_{lim} (table 1). Gas exchange and ventilatory patterns during exercise are shown in table 1. NIRS data were not available in three patients, due to technical reasons. HbO_2 was significantly different between low-frequency, high-frequency and sham TENS at isotime, mainly due to a significant difference between low-frequency and sham TENS ($p<0.05$). A similar trend was observed at t_{lim} ($p=0.06$). Finally, a trend toward an improved S_{tO_2} for low-frequency TENS was also observed at t_{lim} (table 1).

Our study did not show any improvement in endurance exercise capacity with either high-frequency or low-frequency TENS. Overall metabolism and exercise ventilation tended to increase with low-frequency TENS while NIRS revealed that local rectus femoris oxygenation tended to improve with both currents. The lack of effects observed with high-frequency TENS may be related to an activation of specific opioid receptor. While both the fentanyl and low-frequency TENS activate the same μ-opioid receptors, high-frequency TENS effects are mediated through the δ-opioid receptor [4]. NIRS data are frequently used as an indirect surrogate for muscular oxygenation [7]. Therefore, the present results suggest that TENS might improve the ratio between local oxygen delivery and consumption. Among potential mechanisms, an improvement in local oxygen supply through a TENS-mediated sympathovagal modulation may improve vascular conductance and local blood flow [8]. Alternatively, TENS may have change spatial recruitment (out of the range of the superficial NIRS area of interrogation) or the type of muscle fibres recruitment during exercise [9]. A shift toward the recruitment of fast twitch muscular fibres (type II), which are energetically less efficient, would contribute to explain the concomitant increase in metabolism observed with low-frequency TENS [10].

In conclusion, this study does not provide substantive clinical or physiological argument for a positive effect of lumbar TENS on exercise endurance capacity in stable COPD patients.

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The protocol was prospectively registered on www.clinicaltrials.gov (NCT03312322). Data will be shared on request to the corresponding author, for the purposes of meta-analyses.

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II.5. Discussion et conclusion de la seconde partie

Au cours de la BPCO, la réhabilitation respiratoire permet d'améliorer significativement les principaux symptômes du handicap ventilatoire (dyspnée et limitation des capacités fonctionnelles) tout en améliorant la qualité de vie des patients. Cependant, les modalités optimales de réentrainement à l'exercice restent à déterminer. Bien que l'entrainement à haute intensité semble particulièrement efficace, il est souvent mal toléré en raison de la dyspnée et de la limitation ventilatoire à l'effort. Dans ce cadre, des outils existants ou de nouveaux outils peuvent être utilisés pour diminuer la dyspnée et permettre un travail musculaire plus important (183).

Ainsi, à travers une étude prospective randomisée en cross-over menée chez 21 patients non éligibles à la ventilation non invasive au long cours, nous avons montré que celle-ci diminuait la tolérance à l'exercice en endurance à haute intensité. De plus, la ventilation non invasive n'a apporté aucun bénéfice clinique en terme de dyspnée. En raison de la complexité de sa mise en place et des nombreux paramètres susceptibles d'influencer son efficacité, la ventilation non invasive durant l'effort est depuis plusieurs dizaines d'années un sujet de débat avec des résultats variables, particulièrement lorsqu'elle est utilisée au cours d'un programme complet de réhabilitation. Ainsi, les études physiologiques aiguës déjà réalisées ont, pour la plupart, rapporté des effets positifs sur la capacité à l'exercice (142, 144, 149-151) ou aucun effet positif (152, 153), alors que les études à long terme restent non concluantes (119, 120, 154). Dans ce contexte, l'effet négatif retrouvé dans notre contribution originale est inattendu et il est donc difficile de différencier une réelle détérioration de la capacité à l'exercice d'une absence d'amélioration (possibilité d'une erreur statistique de type 1). Malgré cela, notre étude présente plusieurs points forts méthodologiques par rapport à la littérature existante. Tout

d'abord, les tests ont été réalisé dans des conditions semblables à la pratique clinique lorsque la ventilation non invasive est utilisée pour permettre de soutenir un exercice à haute intensité au cours d'un programme de réhabilitation respiratoire. Les résultats négatifs observés à haute intensité n'excluent cependant pas un effet possible à plus faible intensité, suggérant que la ventilation non invasive pourrait être utilisée pour initier la réhabilitation et ainsi atteindre plus rapidement la durée d'entrainement prescrite plutôt que pour atteindre des intensités d'entrainement plus élevées. De plus, cette étude propose l'évaluation de plusieurs facteurs (type de masque, analyses des asynchronismes patient-ventilateur ainsi que des performances du ventilateur), ayant peu fait l'objet de travaux jusqu'à présent. Nos données retrouvent une proportion plus importante d'asynchronismes patient-ventilateur avec le masque nasal qu'avec le masque oronasal (13% contre 3% respectivement, $p<0.01$) et l'analyse des données du ventilateur (pression et débit) suggèrent qu'une limitation technologique de celui-ci est susceptible d'avoir contribué à la diminution de la capacité à l'exercice des patients.

Malgré cela, certaines limites sont à considérer, comme l'absence de double aveugle (aussi bien des patients que des évaluateurs) ou encore l'analyse des mesures de pression et de débit réalisée à partir du pneumotachographe du ventilateur et non pas à partir de capteurs externes. Enfin, l'ordre des tests n'a pas été randomisé, puisque le test en ventilation spontanée a toujours été réalisé en premier afin de permettre un premier ancrage de la perception de l'effort, qui a ensuite servi pour la titration des réglages de la VNI. Malgré cela, un effet d'apprentissage aurait plutôt eu tendance à améliorer les tests suivants, ce qui n'a pas été observé dans cette étude.

Dans un second temps, nous avons montré à travers une étude randomisée multicentrique (avec évaluateurs non informés de l'allocation des patients) que l'ajout d'électrostimulation excito-motrice en autonomie à domicile ne permettait pas d'améliorer la

capacité fonctionnelle à l'exercice (test de marche de six minutes), la capacité maximale à l'exercice (consommation pic en oxygène (VO2pic) et puissance maximale), la dyspnée fonctionnelle ou encore la qualité de vie (Saint George's Respiratory questionnaire) au décours du programme de réhabilitation respiratoire. Ces résultats sont à nuancer au regard des limites de l'étude, notamment un nombre important d'abandon, bien que similaire entre les groupes et identique à d'autres études concernant la réhabilitation respiratoire (184, 185). Malgré cela, un calcul de puissance *post-hoc* sur l'effectif analysé révèle une puissance de 76% à un niveau de significativité statistique de 0,05 (pour une différence moyenne de 35 m (écart-type 44) entre les groupes sur le test de marche de 6 minutes). Enfin, aucun critère musculaire n'a été considéré dans cette étude mais aurait pu révéler une possible amélioration après application de l'électrostimulation. Néanmoins, même si un tel critère avait révélé une amélioration de la fonction musculaire, cela n'aurait pas rendu les résultats cliniquement pertinents pour le patient, du fait que ni la qualité de vie ni les capacités fonctionnelles ne se sont améliorées.

Enfin, dans une dernière étude randomisée durant laquelle patients et évaluateurs n'étaient pas informés du type de courant utilisé, nous n'avons pu montrer que la stimulation électrique nerveuse transcutannée avait des effets cliniques positifs (capacité à l'exercice en endurance, dyspnée ou encore sur la fatigue) bien que des effets physiologiques significatifs aient été retrouvés (augmentation de la VO2 avec le courant à basse fréquence et tendance à l'amélioration de l'oxygénation musculaire périphérique avec les deux types de courant) lors de son utilisation au cours de l'exercice à charge constant à haute intensité chez des patients atteints de BPCO sévère à très sévère. Cela pourrait s'expliquer par un certain nombre de limites, dont le très faible effectif (manque de puissance statistique) ou encore le fait que la stimulation n'ait été réalisée que 10 minutes avant le début des tests à l'effort, ce qui a pu être trop court pour permettre la libération d'endorphines (186, 187). Enfin, il est possible que

l'augmentation du taux d'endorphine dans le liquide céphalo rachidien ait été marginale comparé à l'injection de fentanyl intrathécal (188).

Au total, les contributions originales de cette seconde partie suggèrent que :

- l'utilisation de la ventilation non invasive au cours de l'effort n'améliore pas la performance à l'exercice à haute intensité de patients atteints de BPCO non hypercapniques, en raison d'une limitation technique du dispositif de ventilation.
- la stimulation excito-motrice réalisée en plus d'un programme de réhabilitation respiratoire n'apporte pas de bénéfice supplémentaire chez des patients atteints de BPCO sévère à très sévère.
- la stimulation électrique nerveuse transcutanée ne reproduit pas les effets du fentanyl intrathécal en terme d'amélioration de la dyspnée et de la performance à l'exercice.

Les futures études devraient poursuivre l'utilisation de la ventilation non invasive avec d'éventuels nouveaux algorithmes et surtout identifier les patients répondeurs. Il en va de même pour la stimulation électrique excito-motrice (patients répondeurs) ou nerveuse transcutanée (effet sur la typologie de fibres recrutées et l'oxygénation au cours de l'effort, influence de la durée de stimulation avant l'effort, de la localisation de la stimulation ainsi que des paramètres de stimulation) afin de conclure sur leurs intérêts potentiels.

Troisième partie

III. Perspectives de recherche

Optimisation de l'accès à la réhabilitation respiratoire

Outils existants et nouveaux outils pour optimiser les effets du réentrainement à l'exercice et le maintien des acquis

Bonnevie T, Smondack P, Elkins M, Gouel B, Medrinal C, Combret Y, et al. Advanced telehealth technology improves in-home pulmonary rehabilitation for people with stable chronic obstructive pulmonary disease: a systematic review. [Submitted]

Bonnevie T, Elkins M, Paumier C, Medrinal C, Combret Y, Patout M, et al. Nasal High Flow for Stable Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis. COPD. 2019;16(5-6):368-77.

III.1. Objectifs de la troisième partie

Les deux premières parties de cette thèse nous ont permis d'aborder différentes problématiques entourant la réhabilitation respiratoire, notamment les difficultés d'accès ainsi que l'utilisation d'outils, nouveaux ou existants, pour optimiser les effets de l'entrainement à l'exercice. Les contributions originales proposées ont permis de répondre, au moins partiellement, à ces problématiques. Néanmoins, ces travaux soulèvent d'autres questions et ouvrent la voie à de nouvelles perspectives de recherche. Par exemple, le haut débit nasal est une modalité d'administration de l'oxygène désormais couramment utilisée dans les services de soins intensifs respiratoirtes et de réanimation mais constitue également une approche émergente dans la prise en charge des patients atteints de BPCO à l'état stable ou au cours de l'effort.

Les objectifs de la troisième partie de cette thèse sont de présenter les travaux que nous développons actuellement dans notre équipe sur les thématiques de l'optimisation de l'accès à la réhabilitation respiratoire et de celle des outils existants et nouveaux outils pour optimiser les effets du réentrainement à l'exercice ou encore le maintien des acquis.

III.2. Optimisation de l'accès à la réhabilitation respiratoire

Les contributions originales de cette thèse ont montré que le test stepper de 6 minutes pouvait être utilisé pour individualiser le réentrainement en endurance, particulièrement pour les patients atteints d'une forme légère à modérée de BPCO. Etant donné les différences d'adaptation à l'effort selon la sévérité des symptômes (189, 190), il nous a semblé important d'évaluer de façon indépendante ces différentes catégories de patients. Aussi, nous avons débuté une nouvelle étude dont l'objectif est d'évaluer l'utilisation du test stepper de 6 minutes pour invidualiser l'entrainement en endurance des patients atteints de BPCO sévère à très sévère (6-minute stepper test and pulmonary rehabilitation in patients with severe to very very severe chronic obstructive pulmonary disease; **NCT04004689**). Pour cela, 80 patients atteints de BPCO sévère à très sévère (selon les critères spirométriques GOLD) réaliseront à la fois une épreuve d'effort incrémentale sur vélo et un test stepper de 6 minutes. Une analyse multivariée sera réalisée pour tenter de prédire les valeurs de fréquence cardiaque et de puissance (watts) obtenues durant le test d'effort sur vélo à partir des données obtenues au cours du test stepper de 6 minutes. De la même façon que pour les patients souffrant d'une forme légère à modérée de la maladie, les résultats attendus sont que le test stepper de 6 minutes permettra de définir une modalité d'entrainement fiable pour les patients adressés en réhabilitation respiratoire.

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: July 1, 2019

ClinicalTrials.gov ID: NCT04004689

Study Identification

Unique Protocol ID:	6STaR-2
Brief Title:	6-minute Stepper Test and Pulmonary Rehabilitation in Patients With Severe to Very Severe Chronicle Obstructive Pulmonary Disease (6STaR-2)
Official Title:	Use of the 6-minute Stepper Test to Individualise Pulmonary Rehabilitation in Patients With Severe to Very Severe Chronicle Obstructive Pulmonary Disease
Secondary IDs:	

Study Status

Record Verification:	July 2019
Overall Status:	Not yet recruiting
Study Start:	August 2019 [Anticipated]
Primary Completion:	June 30, 2022 [Anticipated]
Study Completion:	September 30, 2022 [Anticipated]

Sponsor/Collaborators

Sponsor:	ADIR Association
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: CPP-SC 011/2015 Board Name: Comité de Protection des Personnes Nord-Ouest I Board Affiliation: Comité de Protection des Personnes Nord-Ouest I Phone: 0232888446 Email: cpp.nordouest1@chu-rouen.fr Address: Université de Rouen - Faculté de médecine/pharmacie Batiment D - Administration - Bibliothèque Universitaire 22, Boulevard Gambetta - 3ème étage

76183 Rouen Cedex

Data Monitoring: No

FDA Regulated Intervention: No

Study Description

Brief Summary: Chronicle obstructive pulmonary disease is a worldwide cause of mortality and morbidity. This systemic disease progressively leads to dyspnea, muscle wasting and exercise capacity impairment.

Pulmonary rehabilitation is a cornerstone in the management of these systemic effects. Unfortunately, access to pulmonary rehabilitation is limited for many people who would benefit from it, primarily because of a lack of pulmonary rehabilitation and assessment centers. Optimal assessment should include cardiopulmonary exercise testing to determine both the optimal training settings as well as any cardiopulmonary contraindications to pulmonary rehabilitation. However, this is not available in most centers and when it is, consultations are limited. Therefore, pulmonary rehabilitation is often delayed for several weeks and patients can lose motivation.

In order to promote pulmonary rehabilitation, the incremental cardiopulmonary exercise testing could be replaced by field tests to individualize pulmonary rehabilitation prescription.

The 6-minute stepper test is a new field tool. Its sensitivity and reproducibility have previously been reported in patients with chronicle obstructive pulmonary disease. It is easy to set up in the clinical setting and could be used to individualize pulmonary rehabilitation.

The aim of this study was to develop and validate a prediction equation to set rehabilitation intensity for patients with severe to very severe chronicle obstructive pulmonary disease attending pulmonary rehabilitation, with the use of a simple, readily available field test. Therefore the investigators sought to determine, if it exists, a relationship between the plateau heart rate from the first and last 3 minutes of the 6-minute stepper test and the heart rate from the first ventilatory threshold from the cardiopulmonary exercise testing in order to individualize pulmonary rehabilitation in patients with severe to very severe chronicle obstructive pulmonary disease.

Detailed Description: Experimental design:

The validation of the six-minute stepper test to prescribe endurance training in severe to very severe chronicle obstructive pulmonary disease involves two steps :

1. Patients with severe to very severe chronicle obstructive pulmonary disease who performed an incremental cardiopulmonary exercise testing and are referred to pulmonary rehabilitation will be approached to participate in the study.

   Eligible patients who agree to participate in the study and sign informed consent will perform two six-minute stepper test. Their performance and heart rate (first and last 3minutes) will be compared with those obtained at the first ventilatory threshold from the previously performed incremental cardiopulmonary exercise testing (usually used for the prescription of endurance training in pulmonary rehabilitation) using multiple regression in order to derive a predictive equation.
2. The validity of this predictive equation will be assessed in an independent cross-validation group issued from a completed multicenter observational study (NCT03244137). This cross-validation group will be formed with those patients of this cohort who performed both the

incremental cardiopulmonary exercise testing (and had a determined first ventilatory threshold) and the six-minute stepper test. The heart rate prescription for endurance training from the direct measurement of the the first ventilatory threshold will be compared to the heart rate derived from the 6minute-stepper test using the predictive equation determined in step 1. Data will be compared using the mean absolute difference between both prescriptions and a Bland–Altman analysis.

Conditions

Conditions:	Chronic Obstructive Pulmonary Disease Pulmonary Rehabilitation 6-minute Stepper Test
Keywords:	

Study Design

Study Type:	Observational
Observational Study Model:	Cohort
Time Perspective:	Prospective
Biospecimen Retention:	None Retained
Biospecimen Description:	
Enrollment:	80 [Anticipated]
Number of Groups/Cohorts:	1

Groups and Interventions

Groups/Cohorts	Interventions
Prospective observational cohort Every patient referred to pulmonary rehabilitation program will be eligible. They will perform cardiopulmonary exercise testing prior to join the rehabilitation program. During the first session of pulmonary rehabilitation, they will perform 2 6-minute stepper test with a rest of 20 minutes minimum between each test.	2 times : 6-minute stepper test with a rest of 20min between each test. Patients will perform two 6-minute stepper tests separated by a rest period of at least 20 minutes. The second test will begin when the heart rate and the transcutaneous oxygen saturation values will be returned to baseline values. Standardization of the instructions for the test will be based on the actual guidelines for the 6-minute walk test. The test will be performed in an isolated room in order to avoid noise or external stimuli which can affect performance. The stepper will be placed near a door and the patient was allowed to put a hand on it if out of balance or exhausted. The height of the step will be fixed to 20 cm. A step was defined as the rise and lowering of one foot. The patient was informed of the time each minute. No other encouragement was given. Heart

Groups/Cohorts	Interventions
	rate and transcutaneous oxygen saturation will be continuously recorded by a pulse oximetry.

Outcome Measures

Primary Outcome Measure:

1. Relation between plateau heart rate (bpm) from the first and last 3 minutes of the 6-minute stepper test and heart rate (bpm) from first ventilatory threshold from cardiopulmonary exercise testing.
   Outcome (heart rate) during different tests will be continuously recorded. Relation will be adjusted for age and step count.

   [Time Frame: Heart rate (bpm) will be assessed during cardiopulmonary exercise testing with electrocardiogram. During the 2 6-minute stepper test, heart will be assessed with oximeter. All theses tests wil be carried out in a total time frame of 3 month maximum.]

Secondary Outcome Measure:

2. Relation between minimal SpO2 (%)from the 6-minute stepper test and SpO2 (%) from first ventilatory threshold from cardiopulmonary exercise testing.
   Outcome (SpO2 (%)) during different tests will be continuously recorded. Relation will be adjusted for age en step count.

   [Time Frame: SpO2 will be assessed with oximeter. All theses tests wil be carried out in a total time frame of 3 month maximum.]
3. Diastolic blood pressure (mmHg) before and after every 6-minute stepper test using electrical blood pressure device.
   [Time Frame: The outcome will be assessed before and after every 6-minute stepper test. The 2 6-minute stepper test will be carried out the same day (minimum 20 minute of rest between each test) for a total time frame of 1 day.]
4. Systolic blood pressure (mmHg) before and after every 6-minute stepper test using electrical blood pressure device.
   [Time Frame: The outcome will be assessed before and after every 6-minute stepper test. The 2 6-minute stepper test will be carried out the same day (minimum 20 minute of rest between each test) for a total time frame of 1 day.]
5. Steps during 6-minute stepper test using stepper device.
   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]
6. Dyspnea using the Borg scale.
   Borg scale range from 0 (no breathlessness) to 10 (maximal breathlessness)

   [Time Frame: Dyspnea will be assessed at the end of every tests for a total time frame of 2 hours.]
7. Lower limb fatigue using the Borg scale.
   Borg scale range from 0 (no breathlessness) to 10 (maximal breathlessness)

   [Time Frame: Lower limb fatigue will be assessed at the end of every tests for a total time frame of 2 hours.]

Eligibility

Study Population:	Patients with severe to very severe chronicle obstructive pulmonary disease reffered for pulmonary rehabilitation.
Sampling Method:	Probability Sample
Minimum Age:	18 Years
Maximum Age:	
Sex:	All
Gender Based:	

Accepts Healthy Volunteers: No

Criteria: Inclusion Criteria:

- Age > 18 ans ;
- Chronicle obstructive pulmonary disease stage III/IV (FEV1 < 50%) ;
- Weight ≤ 90kg ;
- Eligible for pulmonary rehabilitation ;
- A first ventilatory threshold has been identified during a previously performed incremental cardiopulmonary exercise testing.

Exclusion Criteria:

- Pregnant woman or likely to be ;
- Patient under guardianship ;
- Contraindication to cardiopulmonary exercise testing ;
- Patient medically treated with heart rate modulator (excluding oral B2-agonist) ;
- Patient treated with pacemaker or defibrillator ;
- History of lower limb impairment (i.e. peripheral artery disease, orthopedic disorder etc.).

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D’autre part, le principal inconvénient de l’utilisation d’un test de terrain pour évaluer les patients est qu’il ne permet qu’une évaluation non spécifique de la capacité fonctionnelle car les paramètres cardiorespiratoires et les échanges gazeux ne sont pas monitorés. Bien que la performance au test stepper de 6 minutes soit liée à la consommation pic en oxygène lors d’un test incrémental sur cycloergomètre (71), une comparaison complète et directe des paramètres cardiopulmonaires et des échanges gazeux durant ces deux tests n’a jamais été réalisée. De plus, le test stepper de 6 minutes est plus proche des activités du quotidien (comme la marche ou les montées d’escaliers, nécessitant des transitions répétées entre le repos et une intensité d’exercice sous maximale) que l’épreuve d’effort cardiorespiratoire incrémentale et pourrait ainsi offrir des informations importantes sur les difficultés des patients durant leurs activités habituelles. Enfin, l’analyse des paramètres d’adaptation à l’effort (constante de temps, amplitude et plateau lors de l’analyse de la cinétique de phase deux de la consommation en oxygène) est surtout possible durant des tests à charge constante (191-199), ce qui est le cas du test stepper de 6 minutes. L’analyse de ces paramètres est particulièrement pertinente car elle est indépendante de la motivation du patient ou des critères utilisés pour déterminer l’arrêt de l’exercice. Ainsi, le test stepper de 6 minutes pourrait être utilisé en laboratoire pour obtenir une évaluation plus proche du quotidien des patients tout en étant moins influencée par leur participation.

Ainsi, nous avons débuté une autre étude dont l’objectif principal est de comparer les paramètres cardiorespiratoires, les échanges gazeux ainsi que le niveau de maximalité entre le test stepper de 6 minutes et l’épreuve d’effort cardiorespiratoire incrémentale sur cycloergomètre. Les objectifs secondaires sont de comparer les paramètres de la cinétique de phase deux de la consommation en oxygène selon la sévérité de la pathologie (Comparison of the cardiopulmonary ans gaz-exchange response between the six(minute stepper test and the

incremental cardiopulmonary exercise testing in patients with chronic obstructive pulmonary disease; **NCT04004689**).

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: July 2, 2019

ClinicalTrials.gov ID: [Not yet assigned]

Study Identification

Unique Protocol ID:	PH-6MST
Brief Title:	Comparison of the Cardiopulmonary and Gaz-exchange Response Between the Six-minute Stepper Test and the Incremental Cardiopulmonary Exercise Testing in Patients With Chronicle Obstructive Pulmonary Disease (PH-6MST)
Official Title:	Comparison of the Cardiopulmonary and Gaz-exchange Response Between the Six-minute Stepper Test and the Incremental Cardiopulmonary Exercise Testing in Patients With Chronicle Obstructive Pulmonary Disease
Secondary IDs:	

Study Status

Record Verification:	July 2019
Overall Status:	Not yet recruiting
Study Start:	August 1, 2019 [Anticipated]
Primary Completion:	June 30, 2022 [Anticipated]
Study Completion:	September 30, 2022 [Anticipated]

Sponsor/Collaborators

Sponsor:	ADIR Association
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: CPP-SC 011/2015 Board Name: Comité de Protection des Personnes Nord-Ouest I Board Affiliation: Comité de Protection des Personnes Nord-Ouest I Phone: 0232888446 Email: cpp.nordouest1@chu-rouen.fr Address: Université de Rouen - Faculté de médecine/pharmarcie

Batiment D - Administration - Bibliothèque Universitaire
22, Boulevard Gambetta - 3ème étage
76183 Rouen Cedex

Data Monitoring: No

FDA Regulated Intervention: No

Study Description

Brief Summary: Chronicle obstructive pulmonary disease is a worldwide cause of mortality and morbidity. This systemic disease progressively leads to dyspnea, muscle wasting and exercise capacity impairment.

Pulmonary rehabilitation is a cornerstone in the management of these systemic effects. Unfortunately, access to pulmonary rehabilitation is limited for many people who would benefit from it, primarily because of a lack of pulmonary rehabilitation and assessment centers. Optimal assessment should include an incremental cardiopulmonary exercise testing. This test allows to evaluate the factors contributing to exercise intolerance by linking performance and physiological parameters to the underlying metabolism. Moreover, it is the standard test to determine both the optimal training settings as well as any cardiopulmonary contraindications to pulmonary rehabilitation. However, this test is not available in most centers and when it is, consultations are limited. Therefore, pulmonary rehabilitation is often delayed for several weeks and patients can lose motivation.

In order to promote pulmonary rehabilitation, the incremental cardiopulmonary exercise testing could be replaced by field tests to individualize pulmonary rehabilitation prescription.

The six-minute stepper test is a new field tool. Its sensitivity and reproducibility have previously been reported in patients with chronicle obstructive pulmonary disease. It is easy to set up in the clinical setting and could be used to individualize pulmonary rehabilitation.

The main drawback when using field test is that they only provide a non specific assessement of the functional capacity because cardiopulmonary parameters and gaz exchanges are not monitored.

Although the performance during the 6-minute stepper test is moderately related with the maximal oxygen consumption during the incremental cardiopulmonary exercise testing performed on a cycloergometer, a direct comprehensive comparison of cardiopulmonary parameters and gaz exchanges during these two tests have never been performed.

Moreover, stepping is more closely related with activities of daily life (requiring a repetitive transition from rest to submaximal exercise intensity) than the maximal incremental exercise on cycloergometer and could provide further insight on the disability of patients during their usual activities, such as stair climbing (which is frequently avoided). Additionally, on-transient phase two oxygen consumption kinetic is particularly relevant because it evaluation is independent of the patient's motivation or criteria used to terminate exercise.

Therefore, the aim of this study is to compare the cardiorespiratory parameters, the gaz exchanges and the maximality between the six-minute stepper test and the incremental cardiopulmonary exercise testing performed on a cycloergometer.

The secondary objective was to compare the on-transient oxygen consumption phase two kinetic parameters (time constant, span and steady state) according to the severity of the disease.

Detailed Description: Experimental design:

This study is a pre-specified ancillary study to two other studies (with exactly the same design but a different population) aimed to assess the usability of the six-minute stepper test to prescribe endurance training in patients with mild to moderate (NCT02842463) and severe to very severe (NCT04004689) chronicle obstructive pulmonary disease respectively.

Patients already participating in one of these studies will be approached and offered to participate in an additional testing session (on a different day) using exactly the same procedure but monitoring cardiopulmonary parameters and gaz exchanges using a face mask, a pneumotachograph and a gaz analyser (indirect calorimetry).

Data from these additional two six-minute stepper tests will be compared with those obtained from the previously performed incremental cardiopulmonary exercise testing.

According to the American Thoracic Society and American College of Chest Physicians statement on cardiopulmonary exercise testing, maximality will be considered if either one or more of the following criteria occured:

1. The patient achieves predicted peak oxygen uptake and/or a plateau is observed.
2. Predicted maximal heart rate is achieved (>90%)
3. There is evidence of ventilatory limitation (breathing reserve <11liters or < 15%)
4. Respiratory exchange ratio > 1.15
5. Patient exhaustion/Borg Scale rating of 9–10 on a 0-to-10 scale.

Phase II oxygen consumption kinetics will be modelized by averaging the breath by breath measurement over consecutive periods of 5s for using the following monoexponential equation :

VO2 (τ) = VO2rest + VO2ss – VO2rest))*(1-e-t/τ). with " VO2rest " representing the baseline level of VO2 at rest, " VO2ss " representing the steady state of VO2 during exertion and τ (time constant) representing the time course of the monoexponential VO2 curve. The amplitude of the VO2 (VO2span) corresponds to the difference between VO2ss and VO2rest.

A curve by curve analysis will be performed across participants and parameters (time constant, span and steady state oxygen consumption) will be compared according to the stage of severity.

Conditions

Conditions: Chronic Obstructive Pulmonary Disease
Pulmonary Rehabilitation
6-minute Stepper Test

Keywords:

Study Design

Study Type: Observational

Observational Study Model: Cohort

Time Perspective: Prospective

Biospecimen Retention: None Retained

Biospecimen Description:

Enrollment: 80 [Anticipated]

Number of Groups/Cohorts: 1

Groups and Interventions

Groups/Cohorts	Interventions
Prospective observational cohort Every patient referred to pulmonary rehabilitation program will be eligible. They will perform cardiopulmonary exercise testing prior to join rehabilitation program. During the first session of pulmonary rehabilitation, they will perform 2 6-minute stepper test with a rest of 20 minutes minimum between each test. For the purpose of this study, patients will be offered to participate in an additional exercise session in which they will repeat the same procedure (two 6-minute stepper test) but but monitoring cardiopulmonary parameters and gaz exchanges using a face mask, a pneumotachograph and a gaz analyser (indirect calorimetry).	2 times : 6-minute stepper test with cardiorespiratory parameters and gaz exchange monitoring (with a rest of 20min between each test). For the 6-minute stepper test, please refer to NCT02842463 and NCT04004689. Gaz exchange analyzer will be calibrate before every test. Data will be recorded breath by breath. Heart rate will be monitored using a 12-lead electrocardiogram. Transcutaneous oxygen saturation will be assessed using a pulse oxymetry system at the earlobe.

Outcome Measures

Primary Outcome Measure:

1. Oxygen consumption using indirect calorimetry
   The tests will be performed using a face mask, a pneumotachograph and a gaz analyzer.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

Secondary Outcome Measure:

2. Steps during 6-minute stepper test using stepper device.
   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]
3. Carbon dioxide production using indirect calorimetry
   The tests will be performed using a face mask, a pneumotachograph and a gaz analyzer.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]
4. Heart rate using a 12-lead electrocardiogram
   Heart rate wil be continuously monitored throughout the tests.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]
5. Transcutaneous oxygen saturation using a pulse oxymetry system
   Transcutaneous oxygen saturation will be continuously monitored throughout the tests at the earlobe.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]
6. Tidal volume using a pneumotachograph
   The outcome will be continuously monitored throughout the tests.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

7. Respiratory rate using a pneumotachograph
   The outcome will be continuously monitored throughout the tests.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

8. Minute ventilation using a pneumotachograph
   The outcome will be continuously monitored throughout the tests.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

9. Respiratory exchange ratio using indirect calorimetry
   The outcome will be continuously monitored throughout the tests.

   [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

10. Oxygen equivalent using indirect calorimetry
    The outcome will be continuously monitored throughout the tests and calculated as the ratio between minute ventilation to oxygen consumption

    [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

11. Carbon dioxide equivalent using indirect calorimetry
    The outcome will be continuously monitored throughout the tests and calculated as the ratio between minute ventilation to carbon dioxide production

    [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

12. Ratio between dead space volume to tidal volume using a pneumotachograph and indirect calorimetry
    The outcome will be continuously monitored throughout the tests.

    [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

13. Dyspnea using the Borg scale
    Borg scale range from 0 (no breathlessness) to 10 (maximal breathlessness)

    [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

14. Lower limb fatigue using the Borg scale
    Borg scale range from 0 (no breathlessness) to 10 (maximal breathlessness)

    [Time Frame: The 2 6-minute stepper test will be carried out on the same day (20 minute of rest between each test) for a total time frame of 1 day.]

Eligibility

Study Population:	Patients with chronicle obstructive pulmonary disease reffered for pulmonary rehabilitation.
Sampling Method:	Probability Sample
Minimum Age:	18 Years
Maximum Age:	
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria:

- Age > 18 ans ;
- Chronicle obstructive pulmonary disease stage I/IV ;
- Weight ≤ 90kg ;
- Eligible for pulmonary rehabilitation.

Exclusion Criteria:

- Require during exercise oxygen ;
- Pregnant woman or likely to be ;
- Patient under guardianship ;
- Contraindication to cardiopulmonary exercise testing ;
- Patient medically treated with heart rate modulator (excluding oral B2-agonist) ;
- Patient treated with pacemaker or defibrillator ;
- History of lower limb impairment (i.e. peripheral artery disease, orthopedic disorder etc.).

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Enfin, le modèle proposé au cours de cette thèse consiste à délocaliser le programme de réhabilitation respiratoire afin de le rendre possible en cabinet de kinésithérapie de ville ou au domicile des patients avec l'aide des technologies de santé : on évoque alors le terme de télé réhabilitation (200). Cependant, cette définition est quelque peu confuse dans la mesure où elle englobe des interventions très variées, allant de séances supervisées et monitorées en temps réel par vidéoconférence (78) à un entrainement non supervisé associé à un suivi téléphonique (184), ce qui recoupe la définition de la réhabilitation à domicile conventionnelle. Aussi, nous proposons le terme de « technologies de santé avancées pour délivrer la réhabilitation respiratoire » afin de désigner toute intervention dont l'objectif est d'offrir un service de réhabilitation respiratoire à domicile par l'intermédiaire de technologies de santé plus développées que le suivi téléphonique ou un podomètre seul. Cette approche pourrait permettre un suivi et un service équivalents à ceux proposés au cours des séances de réhabilitation respiratoire réalisées en centre en permettant un feedback direct, rapide ou automatique pour individualiser l'entrainement tout en assurant un niveau de sécurité équivalent. Cela pourrait également permettre l'entrainement des patients plus sévères à domicile (110, 201). A ce jour, il existe peu de données évaluant de tels programmes. De plus, les revues de la littérature sur le sujet considèrent conjointement la réadaptation cardiaque et la réhabilitation respiratoire (200, 202), sont clairement limitées sur le plan méthodologique (203) et n'explorent pas la littérature au-delà de 2015 (202). Etant donné le caractère récent de cette approche et le nombre croissant de publications sur le sujet ces dernières années, il semblait nécessaire de mettre à jour les connaissances concernant l'intérêt d'utiliser de telles technologies pour délivrer la réhabilitation respiratoire pour les patients atteints de BPCO par rapport à 1) l'absence de réhabilitation, 2) la réhabilitation en centre, 3) la réhabilitation à domicile. Dans la mesure où l'utilisation de ces nouvelles technologies peut représenter un coût additionnel par rapport aux programmes à domicile, particulièrement lorsqu'un minimum de ressources est utilisée (184,

204, 205), de tels programmes devraient offrir davantage de bénéfices. Aussi, en tant qu'étape préliminaire à de futurs travaux de recherche sur le sujet, nous avons effectué une revue systématique et une méta-analyse afin de répondre aux questions suivantes (**PROSPERO**) :

- l'utilisation des technologies de santé avancées pour délivrer la réhabilitation respiratoire à domicile est-elle efficace pour les patients atteints de BPCO comparé à l'absence de réhabilitation respiratoire ?
- l'utilisation des technologies de santé avancées pour délivrer la réhabilitation respiratoire à domicile permet-elle une prise en charge aussi efficace qu'en centre (hospitalisation ou ambulatoire) pour les patients atteints de BPCO ?
- l'utilisation des technologies de santé avancées pour délivrer la réhabilitation respiratoire à domicile est-elle plus efficace que la réhabilitation à domicile n'utilisant pas de telles technologies ?

Les revues systématiques et méta-analyses ont pour objectif de regrouper toutes les preuves qui correspondent à des critères d'éligibilité pré spécifiés afin de répondre à une question de recherche. Elles cherchent à minimiser les biais en utilisant une méthode systématique et explicite afin de permettre une conclusion fiable et ainsi des prises de décision (206). Les étapes clés d'une revue systématique sont les suivantes :

- détermination d'objectifs avec critères d'éligibilité des études prédéfinis ;
- méthodologie explicite et reproductible ;
- recherche systématique tentant d'identifier toutes les études qui correspondent aux critères d'éligibilité pré spécifiés ;
- évaluation de la validité des résultats des études inclues (évaluation du risque de biais) ;

- présentation et synthèse systématique des caractéristiques et des résultats des études inclues ;
- utilisation de méthodes statistiques pour résumer les résultats des études indépendantes et ainsi améliorer la précision des estimations (méta-analyse) ;
- synthèse des résultats avec évaluation de la qualité du niveau de preuve (*Grading system for evidence and recommendations*) (206).

Étude n°9

Utilisation des technologies de santé avancées pour la mise en place de la réhabilitation à domicile : Revue systématique et méta-analyse

Advanced telehealth technology improves in-home pulmonary rehabilitation for people with stable chronic obstructive pulmonary disease: a systematic review.

T. Bonnevie, P. Smondack, M. Elkins, B. Gouel, C. Médrinal, Y. Combret, JF. Muir, A. Cuvelier, G. Prieur, FE. Gravier.FE.

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Advanced telehealth technology improves in-home pulmonary rehabilitation for people with stable chronic obstructive pulmonary disease: a systematic review

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Abstract:	Questions How effective is in-home pulmonary rehabilitation delivered using advanced telehealth technology (ATT-PR) for people with chronic obstructive pulmonary disease (COPD), compared with no pulmonary rehabilitation (PR)? How effective is ATT-PR for people with COPD, compared with in/outpatient PR? How effective is ATT-PR for people with COPD, compared with home-based PR not using such technologies? Design Systematic review and meta-analysis of randomised trials. Participants People with stable COPD referred for PR. Intervention ATT-PR. Outcome measures Exercise capacity, quality of life, functional dyspnea, cost-effectiveness, health status, physical activity, acute exacerbations of COPD, hospitalisation and adverse event. Results The 34 eligible records reported on 15 trials involving 1522 participants. Compared with no PR, ATT-PR improved exercise capacity (meta-analysis of four studies, 6-minute walk test MD 15 m, 95% CI 5 to 24), physical activity (four studies, MD 946 steps/d, 95% CI 425 to 1466), and probably also quality of life (four studies, SMD 0.22,

	95% CI 0.00 to 0.43). Compared with in/outpatient PR, ATT-PR had similar outcomes. Compared with conventional home-based PR, ATT-PR produced greater improvement in physical activity (one study, MD 804 steps/d, 95% CI 105 to 1503), a similar or better effect on quality of life (three studies, SMD 0.79, 95% CI –0.04 to 1.62), and similar/uncertain effects on other outcomes. Conclusion ATT-PR improves, exercise capacity, physical activity and quality of life. Its benefits are not inferior to in/outpatient PR and may surpass the benefits of conventional home-based PR. Study registration PROSPERO CRD42020165773.
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ABSTRACT

Questions: How effective is in-home pulmonary rehabilitation delivered using advanced telehealth technology (ATT-PR) for people with chronic obstructive pulmonary disease (COPD), compared with no pulmonary rehabilitation (PR)? How effective is ATT-PR for people with COPD, compared with in/outpatient PR? How effective is ATT-PR for people with COPD, compared with home-based PR not using such technologies? **Design:** Systematic review and meta-analysis of randomised trials. **Participants:** People with stable COPD referred for PR. **Intervention:** ATT-PR. **Outcome measures:** Exercise capacity, quality of life, functional dyspnea, cost-effectiveness, health status, physical activity, acute exacerbations of COPD, hospitalisation and adverse event. **Results:** The 34 eligible records reported on 15 trials involving 1522 participants. Compared with no PR, ATT-PR improved exercise capacity (meta-analysis of four studies, 6-minute walk test MD 15 m, 95% CI 5 to 24), physical activity (four studies, MD 946 steps/d, 95% CI 425 to 1466), and probably also quality of life (four studies, SMD 0.22, 95% CI 0.00 to 0.43). Compared with in/outpatient PR, ATT-PR had similar outcomes. Compared with conventional home-based PR, ATT-PR produced greater improvement in physical activity (one study, MD 804 steps/d, 95% CI 105 to 1503), a similar or better effect on quality of life (three studies, SMD 0.79, 95% CI –0.04 to 1.62), and similar/uncertain effects on other outcomes. **Conclusion:** ATT-PR improves, exercise capacity, physical activity and quality of life. Its benefits are not inferior to in/outpatient PR and may surpass the benefits of conventional home-based PR.

Study registration: PROSPERO CRD42020165773.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a major cause of disability and mortality worldwide with a growing burden.[1,2] This progressive respiratory disease leads to physical inactivity, muscle deconditioning, worsening dyspnoea and reduced quality of life.[3] There is Level 1 evidence that pulmonary rehabilitation (PR) cost-effectively improves exercise capacity, dyspnoea and quality of life, regardless of disease severity.[4,5] Paradoxically, despite this high level of evidence supporting the use of PR, as little as 5% of those people who would benefit from it actually engage in such a program.[6-8] This is explained by a low referral rate (< 15%)[8,9] and a high rate of non-attendance (up to 50%).[10] Moreover, among those people who attend PR, as much as one-third will not complete their program.[10]

A common factor associated both with non-attendance and non-completion of PR is the limited availability of PR centres and transport issues.[9-11] Home-based PR may address these difficulties. Recent meta-analyses have shown that it may be an effective alternative to traditional in/outpatient PR.[12-14]

The term telerehabilitation has been used to describe the delivery of a PR service using telecommunication technology.[15] However, this definition is quite confusing because it includes a wide range of interventions, ranging from real-time supervised and monitored exercise sessions[16] to unsupervised training and phone as a way to follow-up participants,[17] which overlap with more conventional home-based PR. Therefore, we use the term advanced telehealth technology PR (ATT-PR) to describe delivery of in-home PR using any more advanced telehealth technology than phone contact or pedometer alone. The ATT-PR approach enables: the peer support that in/outpatient PR provides; direct, prompt or automated feedback to individualise training; and monitoring for safety, adherence and early signs of

exacerbations.[18,19] Although ATT-PR uses new technologies, it has been shown to be feasible and well accepted by people attending PR.[19,20]

Because ATT-PR uses new technologies, it may incur an additional burden and cost compared with conventional home-based PR, particularly home-based PR that uses minimal resources.[17,21,22] To be considered worthwhile, ATT-PR therefore needs to provide further advantages over conventional home-based PR.

To date, systematic reviews on the topic have considered both cardiac and pulmonary rehabilitation,[15,23] had methdological limitations,[24] and/or not included research published after 2015.[23] Therefore, there is a need to summarise current evidence about the effects of ATT-PR for people with COPD compared with no PR, in/outpatient PR or conventional home-based PR (ie, without ATT).

Therefore, the research questions for this systematic review were:

1. How effective is ATT-PR for people with COPD, compared with no PR?
2. How effective is ATT-PR for people with COPD, compared with in/outpatient PR?
3. How effective is ATT-PR for people with COPD, compared with home-based PR not using such technologies?

METHOD

The prospectively registered protocol of this systematic review was designed according to the Cochrane Handbook for Systematic Reviews of Interventions and is reported according to the PRISMA statement.[25]

Criteria for considering studies for this review

Types of studies

Only parallel and cross-over randomised trials were eligible for inclusion in the review. Trials reported in English, French, Spanish or Portuguese were eligible, regardless of whether the report was full text or abstract only.

Type of participants

Trials were only eligible for inclusion if the participants were people of any age with stable COPD (no acute exacerbation in the previous 4 weeks, where an exacerbation was defined according to the individual study's criteria). Studies with a mixed population of COPD and other respiratory disease(s) or with a mixed population of stable and non-stable COPD could be included if the data for the participants with stable COPD could be extracted separately or accounted for more than 95% of the data.

Type of intervention

Trials were only eligible if they assessed the effects of initial in-home PR delivered using advanced telehealth technology. Trials were ineligible if they examined pedometer-based intervention or phone contact without additional telehealth technology to follow participants and adapt individualised goals.

According to McCarthy et al,[4] PR is defined as any program with a duration of at least 4 weeks that includes exercise therapy with or without any form of education and/or psychological support delivered to patients with exercise limitation attributable to COPD. Exercise therapy had to be aerobically demanding and therefore respiratory muscle training,

breathing exercise, Tai Chi and yoga interventions were not eligible as the exercise intervention. Maintenance programs following initial PR were also excluded.

Type of comparator

Three types of comparator were considered and analysed separately: no PR, in/outpatient PR, and home-based PR (ie, conventional home-based PR that does not use ATT).

Type of outcome measures

The primary outcomes are listed in Box 1. The secondary outcomes are listed in Box 2.

Search methods for identification of studies

Electronic searches

MEDLINE, CENTRAL, Science Direct, Scopus, PEDro, Greylist and OpenGrey were searched from inception up to May 2020 for relevant studies. Additional handsearching was performed through the abstracts of the European Respiratory Society congress from 2011 to 2019 and through the abstracts of the American Thoracic Society congress from 2009 to 2019. Reference lists of the included studies and relevant systematic reviews were also checked for additional eligible studies.

The electronic search strategy used a sensitivity-maximising method to combine search terms related to: COPD or chronic lung disease; telehealth or telerehabilitation; home care; technology; pulmonary rehabilitation or exercise training; and methods of remote contact, such as videoconferencing, phone-based and web-based. For the detailed search strategy, see Appendix 1 on the eAddenda.

Data collection and analysis

Selection of studies

Two authors (TB, FEG) independently assessed the retrieved studies for eligibility. Any disagreement was resolved by discussion and the intervention of a third author (CM). The level of agreement was assessed using a kappa statistic.

Data extraction and management

Two authors from a pool of three (TB and FEG or PS) independently extracted data about the study characteristics and outcomes using a standardised form. For continuous outcomes, mean (SD) change from baseline and/or mean (SD) post-treatment values for each group were extracted. When the data were not available in another format, they were extracted from graphs using software[a]. Skewed data were converted into mean (SD).[26,27] The number of events was recorded for count outcomes.

Data from cross-over studies were managed according to the Cochrane Handbook for Systematic Reviews of Interventions.[25] Studies were pooled if they had the same comparator intervention: no PR, in/outpatient PR, or home-based PR without ATT. For outcomes measured multiple times, matched time points were considered for analysis (short-term: 1 to 4 months; long-term: 9 to 12 months).

Assessment of risk of bias in the included studies

Two authors from a pool of three (TB and FEG or PS) independently assessed the methodological quality of the included studies using the methods described in the Cochrane Handbook for Systematic Reviews of Interventions.[25] The methodological criteria included random sequence generation, allocation concealment, blinding, incomplete outcome data,

selective reporting and other potential bias. The risk of bias in the 'blinding' domain may differ between outcomes within a study, even if the same people were aware of intervention assignments during the trial. Therefore, the risk of bias was assessed independently for patient-reported outcomes, observer-reported outcomes involving some judgement, and observer-reported outcomes not involving judgement. Using a conservative approach, the highest risk of bias for any outcomes measured within a given study was reported as the main author's judgement risk of bias. Any disagreement was resolved by discussion or the intervention of another author (ME).

Measures of treatment effect

The effect of the treatment was estimated by the mean differences (MD) or the standardised mean difference (SMD) for continuous outcomes and risk ratio (RR) for counts, with their corresponding confidence intervals (CIs).

When calculating the SMD: change values and post-treatment values were not pooled, and patient-reported outcomes (such as quality of life) were converted so that a higher score always indicates a better outcome. The clinical usefulness of the estimated treatment effects was assessed according to their respective minimum clinically important difference (MCID) when available: 47 m for the incremental shuttle walk test (ISWT),[28] 25 m for the six-minute walk test (6MWT),[28] 65 s for the endurance shuttle walk test (ESWT),[28] 600 for daily steps count,[29] 2 points for the Chronic Respiratory Questionnaire (CRQ) total score,[30] 0.5 for the dyspnea sub-score,[30] –0.6 points for the Clinical COPD Questionnaire (CCQ),[31] –4% for the Saint George's Respiratory Questionnaire (SGRQ),[30] –2.5 points for the COPD Assessment Test (CAT),[31,32] 1 point for the Pulmonary Rehabilitation Adapted Index of Self-Efficacy (PRAISE),[33] 1 point for the modified Medical Research Council dyspnea scale (mMRC),[34]

and −1.5 for the Hospital Anxiety and Depression scale anxiety and depression sub-scores (HAD-A and HAD-D, respectively).[31]

Dealing with missing data

The impact of missing data was assessed in the 'risk of bias' assessment. Authors from original studies were contacted to obtain complementary data when necessary. Where data could not be included in a meta-analysis, results were reported narratively.

Assessment of heterogeneity

Heterogeneity was assessed using the I^2 and Chi^2 statistic, considering values $I^2 \geq 50\%$ as a sign of moderate to high heterogeneity.

Assessment of publication bias

The protocol for the systematic review stated that this would be assessed by funnel plot if 10 or more studies were available for a given meta-analysis.

Data synthesis

Meta-analysis was performed with a fixed-effect model when heterogeneity was low (< 50%), using the inverse-variance method (for continuous outcome and incidence rates) and the Mantel-Haenszel method (for dichotomous outcomes). In the case of moderate-to-high heterogeneity, a random-effects model was used. Meta-analysis software[b] was used for all analyses. The quality of evidence was rated independently for each outcome by two authors (TB, FEG) using the GRADE system.

Additional analyses

Subgroup analyses were planned to assess the effects of the intervention according to the type of intervention: real-time supervised/monitored exercise sessions; unsupervised training but with a target/imposed tailored intensity and telehealth feedback (eg, walking at a given speed corresponding to X% of VO_2peak); or unsupervised training based on increasing physical activity only (steps/day with automated and tailored goals) and telehealth feedback but without an imposed intensity. A sensitivity analysis was planned to assess the consistency of the results after removing high-bias studies.

RESULTS

Description of studies and participants

After removal of duplicates, 605 records were retrieved from the initial database searching and 1 additional record was found after an update in May 2020. After assessment of eligibility, 15 studies (34 records) were included, involving a total of 1522 participants (Figure 1). There was good agreement between authors for the study selection (kappa 0.96). Characteristics of the included studies (methods, participants, intervention and outcomes) are shown in Table 1.

Fourteen studies were reported as full-text publications[16,35-51] and one was available as an abstract only.[52] ATT-PR was compared with no PR in seven studies,[16,35-37,40,41,52] with in/outpatient PR in three studies,[42-44,51,53,54] and with home-based PR in six studies.[39,45-50] One study compared ATT-PR compared with both no PR and home-based PR.[38] The intervention consisted of real-time supervised/monitored exercise sessions in two studies,[16,51,53,54] unsupervised training but with a target/imposed tailored intensity and telehealth feedback in seven studies,[38-40,42-44,47,48] and unsupervised training based on increasing physical activity only and telehealth feedback but without an imposed intensity in six studies.[35-37,41,45,49,50,52]

The duration of the intervention ranged from 1 to 12 months and the frequency of exercise training varied from 3 to 7 times per week. In all studies, the mean forced expiratory volume in 1 second (FEV_1) was ≥ 30% of the predicted value.

Risk of bias in included studies

The risk of bias among the included studies is shown in Figure 2, with more detail in Appendices 2 and 3 on the eAddenda. Lack of blinding of the participants and outcome assessors were the most common biases. There were not enough studies to construct a funnel plot to assess reporting bias for any outcome.

Effect of ATT-PR compared with no PR

Seven studies involving 787 participants contributed data on the effects of ATT-PR compared with no PR.[16,35-38,40,41,52] The follow-up periods ranged from 1 to 12 months. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) summary of findings table for this comparison is presented in Appendix 4 on the eAddenda.

Exercise capacity

The short-term effect of ATT-PR on exercise capacity was assessed using the ISWT[16] and the 6MWT.[16,35,38,40] Tsai et al (36 participants) estimated that ATT-PR does not improve the ISWT to any worthwhile extent (MD 6 m, 95% CI –23 to 35),[16] while the meta-analysis for the 6MWT (four studies[16,35,38,40] involving 458 participants) found that ATT-PR produced a benefit (pooled MD 15 m) although that benefit is too small to be worthwhile (95% CI 5 to 24, $I^2 = 3\%$, Figure 3A).

One study involving 84 participants assessed the long-term effect of the intervention on the 6MWT. Although the average benefit would be worthwhile (MD 25m), this estimate came with a very high uncertainty (95% CI –28 to 76).[38]

Endurance exercise capacity was assessed in one study involving 36 participants using the ESWT.[16] ATT-PR was estimated to have a very worthwhile positive effect at short-term (MD 340 s, 95% CI 153 to 527).

Quality of life

The short-term effect of ATT-PR on quality of life was assessed using: the CRQ-T, measured from 20 'worst' to 140 'best';[16,38] the CCQ, measured from 0 'best' to 60 'worst';[40,41] and the SGRQ, measured from 0 'best' to 100 'worst'.[36,37] The meta-analysis (4 studies[16,36-38,40] involving 361 participants) found a small positive effect from ATT-PR (pooled SMD 0.22) although the uncertainty around this estimate ranged from no benefit to a moderate benefit (95% CI 0.00 to 0.43, $I^2 = 0\%$, Figure 4A). Converted back to an original unit (SGRQ) using data from an observational study,[31] the estimate revealed a worthwhile improvement (MD –4%) although the uncertainty around this estimate ranged from a clinically trivial benefit to a worthwhile benefit (95% CI –7 to 0). Additionally, one study involving 29 participants found that the effect of ATT-PR on the CCQ is uncertain (MD –0.4, 95% CI –0.8 to 0.1).[41]

The long-term effect of ATT-PR was assessed in two studies, which could not be pooled for meta-analysis. Ngyuen et al[38] (84 participants) estimated that the effect of ATT-PR on the CRQ-T is beneficial but the estimate was very uncertain (MD 6, 95% CI –4 to 16) and Moy et al[37] (229 participants) found no worthwhile effect of ATT-PR on the SGRQ (MD 1%, 95% CI –2 to 4).

Functional dyspnea

The short-term effect of ATT-PR on functional dyspnea was assessed in two studies (which could not be pooled for meta-analysis) using the CRQ-D (5 'worst' to 35 'best')[38] and the mMRC dyspnea score (0 'best' to 4 'worst').[41] One study involving 84 participants produced a very uncertain estimate for the effect on the CRQ-D (MD 2, 95% CI –1 to 4)[38] and the other study, involving 29 participants, estimated that the effect on the mMRC dyspnoea scale is unlikely to be worthwhile (MD 0, 95% –1 to 1).[41] The long-term effect was assessed in one study (84 participants), which reported a very uncertain effect of ATT-PR on the CRQ-D (MD 2, 95% CI –1 to 5).[38]

Health status

The short-term effect of ATT-PR on health status was assessed using the CAT (0 'best' to 40 'worst') in two studies involving 354 participants.[16,55] The meta-analysis estimated that ATT-PR does not improve health status to any worthwhile extent (pooled MD –1, 95% CI –2 to 0, $I^2 = 25\%$).

Quadriceps force

One study involving 318 participants assessed the short-term effect of ATT-PR on quadriceps force using isometric measurement and found that any benefit would be trivial (MD 0 kg, 95% CI –1 to 2).[35]

Objective physical activity

The short-term effect of ATT-PR on physical activity was assessed using steps per day,[16,41,55-57] as well as "activity count" raw unit using various activity monitoring devices.[16,40,52] The

meta-analysis of the effect on steps per day (4 studies[16,41,55-57] involving 510 participants) found a worthwhile positive effect (pooled MD 946 steps/d) although the uncertainty around this estimate ranged from a clinically trivial benefit to a very worthwhile benefit (95% CI 425 to 1466, $I^2 = 53\%$). The meta-analysis of the effects on "activity count" (2 studies[16,52] involving 54 participants) produced a very imprecise estimate (pooled SMD 0.36, 95% CI –0.19 to 0.91, $I^2 = 74\%$). The data from Tabak 2014a was not pooled within the meta-analysis because there was an extreme difference in baseline "activity count" between groups.[40]

One study involving 238 participants estimated that ATT-PR may not improve steps per day to any worthwhile extent in the long-term (MD –108 steps) although there was considerable uncertainty in the estimate (95% CI –720 to 504).

Subjective physical activity

The short-term effect of ATT-PR on subjective physical activity was assessed in two studies (involving 56 participants) using the Functional Performance Inventory-Short Form (0 'worst' to 96 'best'),[16] and the Baecke Physical Activity Questionnaire (3 'worst' to 15 'best').[41] The meta-analysis estimated that there might be a small beneficial effect on subjective physical activity (pooled SMD 0.34) but this estimate came with a very high uncertainty (95% CI –0.19 to 0.87, $I^2 = 11\%$).

Anxiety and depression

One study involving 36 participants contributed data on the short-term effect of the intervention on anxiety and depression using the HAD-A and HAD-D tools respectively (0 'best' to 21 'worst'),[16] and estimated that there may be a worthwhile beneficial effect of ATT-

PR on anxiety and depression (both MD –2) although these estimates came with uncertainty ranging from a clinically trivial benefit to a very worthwhile benefit (both 95% CI –4 to 0).

Self-efficacy

The short-term effect of ATT-PR on self-efficacy was assessed in two studies[16,38] involving 120 participants) using the Pulmonary Rehabilitation Adapted Index of Self-Efficacy (15 'worst' to 60 'best')[16] and a validated question (0 'worst' to 10 'best').[38] The meta-analysis found a moderate positive effect in favour of the intervention (pooled SMD 0.59) although the uncertainty around this estimate ranged from virtually no benefit to a very worthwhile benefit (95% CI 0.02 to 1.17, $I^2 = 51\%$).

The long-term effect was assessed in one study[38] involving 84 participants using a validated question but it generated an imprecise estimate of the effect of the intervention (MD 0.6, 95% CI –0.7 to 1.9).

Acute exacerbation of COPD

The long-term effect was assessed in one study involving 238 participants, which produced an uncertain estimate (RR 1.3, 95% CI 0.7 to 2.2).[36,37]

Hospitalisation

The long-term effects of the intervention on the hospitalisation risk was assessed in two studies involving 262 participants.[40,56,57] The meta-analysis produced an uncertain estimate (pooled RR 1.3, 95% CI 0.9 to 2.1).

Mortality

The long-term effect was assessed in one study[56,57] involving 238 participants, which produced a very imprecise estimate (RR 1.6, 95% CI 0.3 to 7.9).

Withdrawal

Seven studies [16,35,38,40,41,56,57] involving 765 participants produced an imprecise estimate of the effect of the intervention on withdrawal in the short-term (pooled RR 1.1, 95% CI 0.7 to 1.9, $I^2 = 0\%$) and two studies[38,40] involving 113 participants produced a very uncertain estimate of the intervention on withdrawal in the long-term (pooled RR 0.6, 95% CI 0.2 to 1.9, $I^2 = 59\%$).

Adverse events

Three studies[16,35,56,57] involving 582 participants contributed data on the risk of musculo-skeletal adverse events. The meta-analysis estimated a substantial increase in risk associated with the use ATT-PR (pooled RR 5.7, 95% CI 2.5 to 12.9, $I^2 = 0\%$).

One study involving 238 participants also found a substantial increase in risk of musculo-skeletal adverse events associated with the intervention in the long-term (RR 2.9, 95% CI 1.5 to 5.9).[56,57]

Other outcomes

No data were available for cost-effectiveness, respiratory function and adherence.

Effect of ATT-PR compared with in/outpatient PR

Three studies involving 327 participants contributed data on the effects of ATT-PR compared with in/outpatient PR.[42-44,51,53,54] The follow-up periods ranged from 1.5 to 12 months. The

GRADE summary of findings table for this comparison is presented in Appendix 5 on the eAddenda.

Exercise capacity

Two studies involving 224 participants contributed data on exercise capacity in the short-term using the 6MWT. The meta-analysis estimated that the effect of ATT-PR was similar to the effect of in/outpatient PR (pooled MD 6 m) but this estimate came with very high uncertainty (95% CI –26 to 37, $I^2 = 73\%$, Figure 3B).[42,51,53,54]

One study involving 134 participants produced a very uncertain estimate about the relative effect of ATT-PR versus in/outpatient PR on the 6MWT in the long-term (MD 6 m, 95% CI –25 to 36).[53,54]

Endurance exercise capacity was assessed in one study involving 62 participants.[43,44] It estimated that ATT-PR and in/outpatient PR had similar effects on the ESWT in the short-term (1 to 4months) but this was a very uncertain estimate (MD 5 s, 95% CI –112 to 121).

Quality of life

The short-term effects of ATT-PR compared with in/outpatient PR on quality of life was assessed using the SGRQ[42] and the CCQ.[51,53,54] The meta-analysis (2 studies involving 224 participants) found a small relative positive effect from ATT-PR (SMD 0.23) although the uncertainty around this estimate ranged from no benefit to a moderate benefit (95% CI 0.0 to 0.5, $I^2 = 0\%$). Converted back to an original unit (SGRQ) using the SD of 17.1 from an observational study,[31] the estimate revealed a worthwhile relative effect (MD –4%) but this estimate came with uncertainty ranging from a clinically trivial benefit to a very worthwhile benefit (95% CI –9 to 0).

Functional dyspnea

The short-term effect of the intervention compared with in/outpatient PR was assessed using the CRQ-D[43,44] and the mMRC dyspnea scale.[42] The meta-analysis (2 studies involving 152 participants) found similar effect between interventions (pooled SMD –0.05, 95% CI –0.39 to 0.29, $I^2 = 0\%$). Converting this result back to the original units of the mMRC scale using data from an observational study,[58] the estimate revealed that ATT-PR has essentially the same effect as in/outpatient PR (MD 0, 95% CI 0 to 0).

Health status

Two studies study involving 224 participants assessed the short-term effect of the intervention on health status using the CAT and found that ATT-PR was similar to or better than in/outpatient PR (MD –1, 95% CI –3 to 0, $I^2 = 0\%$).[42,51,53,54]

Objective physical activity

One study involving 134 participants found that the relative short-term effect of ATT-PR was similar to or better than in/outpatient PR on steps/day (MD 436, 95% CI –138 to 1010).[51,53,54] Additionally, the same study generated an uncertain estimate regarding active time (MD 7.7 minutes, 95% CI –49 to 52).

Anxiety and depression

One study involving 134 participants assessed the short-term effect of the intervention on anxiety and depression using the HAD-A and HAD-D and estimated that ATT-PR may be slightly better compared with in/oupatient on anxiety and depression (both MD –1). However, the uncertainty around these estimates ranged from no benefit to a worthwhile benefit (95% CI –2 to 0 for each).[51,53,54] Additionally, Bourne et al[42] (90 participants) reported the short-

term HADS total score and estimated that ATT-PR has a similar effect to in/outpatient PR (MD –1, 95% CI –3 to 2).

Adherence

Two studies involving 224 participants produced a very uncertain estimate of the relative effect of the interventions at short-term (RR 1.0, 95% CI 0.9 to 1.3).[42,51,53,54]

Withdrawal

Three studies involving 327 participants contributed data on withdrawal at short-term.[42-44,53,54] The meta-analysis produced a very uncertain estimate of the relative effect of the interventions (pooled RR 1.1, 95% CI 0.3 to 3.4, $I^2 = 88\%$).

Adverse event

Two studies involving 224 participants assessed minor adverse event at short-term and produced a uncertain estimate of the relative effect of the interventions (pooled RR 0.24, 95% CI 0.1 to 1.1).[42,51,53,54]

Other outcomes

No data were available for cost effectiveness, quadriceps force, subjective physical activity, respiratory function, self-efficacy, acute exacerbation of COPD, hospitalisation and mortality.

Effect of ATT-PR compared with home-based PR

Six studies involving 451 participants contributed data on the effects of ATT-PR compared with home-based PR.[38,39,45-50] The follow-up periods ranged from 3 to 12 months. The

GRADE summary of findings table for this comparison is presented in Appendix 6 on the eAddenda.

Exercise capacity

Exercise capacity was assessed using the ISWT[48] and the 6WMT.[38,39,49,50] Although Liu et al[48] (involving 48 participants) found substantially better ISWT results with ATT-PR both at short-term (MD 77 m) and in the long-term (MD 69 m), these estimates came with uncertainty, ranging from trivially better to very markedly better (95% CI 26 to 127 and 95% CI 21 to 118, respectively). The meta-analysis for the 6MWT (3 studies[38,39,49,50] involving 231 participants) estimated a similar relative effect (pooled MD 2 m, 95% CI –16 to 19, $I^2 = 27\%$, Figure 4C). One study involving 84 participants estimated a similar relative effect in the long-term but this was a very uncertain estimate (MD 6 m, 95% CI –46 to 58).[38]

Quality of life

The effect of ATT-PR compared with home-based PR on quality of life was assessed using the Short Form-12 health questionnaire (0 'worst' to 100 'best'),[48] the CRQ-T[38,39] and the SGRQ.[49,50] The meta-analysis (3 studies involving 171 participants) estimated that ATT-PR had a much better effect at short-term (pooled SMD 0.79) but this estimate came with uncertainty ranging from essentially similar effects through to a very worthwhile benefit (95% CI –0.04 to 1.62, $I^2 = 84\%$, Figure 4C). Converted back to an original unit (SGRQ) using the SD of 17.1 from an observational study,[31] the estimate revealed a very worthwhile relative effect (MD –14%) but again with substantial uncertainty (95% CI –28 to 1). Additionnaly, Wan et al[49,50] (involving 109 participants) found a very uncertain relative effect on the SGRQ (MD 0%, 95% CI –5 to 4).

Two studies involving 132 participants estimated that ATT-PR had a markedly better effect on quality of life in the long term (pooled SMD 1.05), although this estimate came with substantial uncertainty (95% CI –0.37 to 2.47).[38,48] Converted back to an original unit (SGRQ), the estimate revealed a very worthwhile benefit (MD –18%) but still with substantial uncertainty (95% CI –42 to 4).

Functional dyspnea

The short-term effects of the interventions on functional dyspnea were assessed using the CRQ-D[38,39] and the mMRC dyspnea score.[49,50] The meta-analysis (2 studies[38,39] involving 123 participants) estimated that ATT-PR had substantially greater benefit on the CRQ-D (MD 2) although the estimate came with uncertainty ranging from a clinically trivial benefit to a very worthwhile benefit (95% CI 0 to 4, $I^2 = 0\%$). Additionaly, Wan et al[49,50] (involving 109 participants) estimated that the effects of the two forms of PR were similar on the mMRC dyspnea score (MD 0, 95% CI –1 to 0).

One study involving 84 participants found a very worthwhile relative effect in the long-term of ATT-PR over home-based PR on the CRQ-D (MD 3), although this estimate came with uncertainty, ranging from no benefit to a very worthwhile benefit (95% CI 0 to 6).[38]

Cost-effectiveness

One study involving 105 participants reports an uncertain relative effect on total cost in the long-term (MD –€288, 95% CI –3998 to 3424) as well as in the incremental quality-adjusted life years (MD 0.03, 95% CI 0 to 0.06).[45,46]

Health status

One cross-over study involving 44 participants estimated that the relative effect of ATT-PR was similar to or better than home-based PR to improve the CAT in the short-term (MD 0, 95% CI –3 to 2).[47]

Objective physical activity

One study involving 109 participants found the ATT-PR had a substantially greater effect on steps/day than home PR in the short term (MD 804 steps). However, this estimate came with uncertainty ranging from a clinically trivial benefit to a very worthwhile benefit (95% CI 105 to 1503).[49,50]

Subjective physical activity

One cross-over study involving 44 participants found uncertain short-term relative effect on the Godin Total Leisure Activity score (measured from 0 to no formal upper limit, higher score indicates higher subjective physical activity) (MD 3, 95% CI –2 to 7).[47]

Anxiety and depression

One study involving 109 participants found that ATT-PR and home PR had very similar short-term effects on the Beck Anxiety Inventory (0 'best' to 63 'worst'), with mean difference of 0 (95% CI –2 to 2).[49,50]

Self-efficacy

Self-efficacy was assessed using one validated question (measured from 0 'worst' to 10 'best')[38,39] and the Exercise Self Regulatory Efficacy scale (measured from 1 'worst' to 160 'best').[49,50] The meta-analysis (2 studies involving 123 participants) estimated that ATT-PR may have a better short-term effect than home PR on the validated question (pooled MD 1,

95% CI 0 to 2, $I^2 = 0\%$). Additionaly, Wan et al (involving 109 participants) did not identify any clear difference on the Exercise Self Regulatory Efficacy scale (MD 4, 95% CI –4 to 12).[49,50] One study involving 84 participants found uncertain relative effect in the long-term between interventions on the validated question (MD 1, 95% CI 0 to 2).[38]

Acute exacerbation of COPD

The long-term effect was assessed in one study involving 48 participants, which estimated a worthwhile relative effect on the risk of acute exacerbations (RR 0.2, 95% CI 0.1 to 0.8) as well as in the incidence rate of exacerbations (Rate Ratio 0.1, 95% CI 0.0 to 0.6).

Hospitalisation

Two studies involving 153 participants estimated an uncertain long-term relative effect in the risk of hospitalisation between interventions (pooled RR 0.5, 95% CI 0.2 to 1.5, $I^2 = 56\%$)[45,46,48] and one study involving 134 participants also found an uncertain relative effect in the time to first hospitalisation (HR 1.2, 95% CI 0.8 to 1.8).[53,54]

Mortality

One study involving 48 participants procuded a very uncertain estimate of the relative effect in the long-term on mortality (RR 0.3, 95% CI 0.0 to 7.8).[48]

Adherence

One study involving 109 participants found an uncertain short-term relative effect in adherence (RR 1.0, 95% CI 0.9 to 1.2),[49,50] but another study involving 48 participants reported a very worthwhile benefit of ATT-PR over home PR on long-term adherence (RR 2.4, 95% CI 1.4 to 4.2).[48]

Withdrawal

One study involving 84 participants produced a very uncertain estimate of the short-term relative effect in withdrawal between interventions (RR 0.2, 95% CI 0.0 to 3.9).[38] The meta-analysis of four studies involving 369 participants produced an uncertain estimate of the long-term relative effect between interventions (pooled RR 1.0, 95% CI 0.5 to 1.9).[38,45,46,48-50]

Adverse event

One study involving 114 participants produced an uncertain estimate of the short-term relative effect in the risk of adverse events (RR 1.3, 95% CI 0.6 to 2.6) as well as in the incidence rate of adverse events (Rate Ratio 1.3, 95% CI 0.6 to 2.6).

Other outcomes

No data were available for quadriceps force or respiratory function.

Additional analyses

Due to the limited number of studies available per outcome, subgroup and sensitivity analysis were not undertaken. However, studies were displayed in their corresponding subgroup to offer further visual insight on the forest plots.

DISCUSSION

The main findings of this systematic review were that: ATT-PR increases exercise capacity, physical activity, self-efficacy and probably quality of life; ATT-PR probably has similar effects as in/outpatient PR on the same patient-centered outcomes; and ATT-PR may be similar to or better than home-based PR (that does not use such technologies) to improve

quality of life, functional dyspnea, physical activity, self-efficacy and the risk of acute exacerbation of COPD.

ATT-PR compared with no PR

Although ATT-PR improved the 6MWT (pooled MD 15 m, 95% CI 5 to 24) and ISWT (MD 6 m, 95% CI –23 to 35), these effects were less than the MCIDs of 25 m and 47 m, respectively.[28] This suggests that the effect of ATT-PR on exercise capacity is unlikely to be clinically worthwhile. Although widely used, the 6MWT is not as responsive as endurance exercise testing to assess exercise capacity following an intervention in COPD patients, which may explain the lack of clinical effect found in the present analysis.[59] This explanation is supported by the fact that Tsai et al[16] found a very worthwhile improvement from ATT-PR on the ESWT, for which the lower bound of the estimates (MD 340 s, 95% CI 153 to 527) greatly exceeds the established MCID for this outcome (65 s).[28]

The estimated effect of ATT-PR on quality of life, when converted back to the original units of the SGRQ, equated to the MCID (–4%),[30] and the 95% CI ranged from no effect to –7%. Further trials could help to refine this estimate.

Unlike conventional exercise training programs, which do not necessarily increase physical activity,[60,61] ATT-PR clearly improved steps per day (pooled MD 946 steps, 95% CI 425 to 1466). The improvement in physical activity may be explained by the fact that ATT-PR may: facilitate the integration of a daily exercise routine; improve self-efficacy to manage dyspnoea (a positive effect also found in the present review); and promote autonomous exercise. Although the lower bound of the 95% CI is below the MCID for steps/day, the effect might be clinically valuable anyway, not only because the mean estimate is higher than the MCID

(+600) but also because increases in physical activity are inversely associated with cardiovascular events, hospitalisations and mortality among COPD patients.[29,62,63] This could not be confirmed because such events were rare in the included studies, leading to imprecise estimates.

Although ATT-PR increased adverse events, these were only minor musculoskeletal events and their occurrence was as frequent (10 to 20%) as in other studies assessing high-risk populations resuming physical activity.[64]

ATT-PR compared with in/outpatient PR

Based on the three available trials, ATT-PR seemed as effective as centre-based PR. The relative estimates between interventions didn't exceed the MCID for any outcomes in favour of centre-based PR, except for exercise capacity, for which the relative effect was very uncertain (see Appendix 5 on the eAddenda). Unless future studies clarify an important difference in their effects, ATT-PR may be a valuable alternative for those people who can not attend centre-based programs.

ATT-PR compared with home-based PR

ATT-PR and home-based PR had similar effects on exercise capacity, as measured using the 6MWT or ISWT. However, the use of advanced telehealth technology during home-based PR may produce greater improvements in quality of life, functional dyspnea and physical activity. Further study should be performed to refine these estimates because their confidence intervals do not exclude the possibility that the effects differ to an important degree. Given this uncertainty, the cost-effectiveness and the cost-utility of adding telehealth technology to

home-based PR (which may be expensive when it includes a laptop computer or a smartphone connected to the internet) also warrant further investigation.

ATT-PR with automated feedback facilitates long-term adherence to exercise training (RR 2.4, 95% CI 1.4 to 4.2),[48] which would be expected to maintain long-term benefit, although this notion has recently been questionned.[65] The use of ATT to maintain exercise training following an initial PR program is a new research area with promising results.[66,67]

Strength and limitations

The strengths of this review include prospective registration, a thorough search strategy, duplicate data processes and minimal language bias. The main risk of bias among the included trials was lack of blinding, although this is common in trials of physical interventions. Despite a substantial pool of included studies, the dataset was insufficient for the planned subgroup and sensitivity analyses. Although the GRADE ratings were very low for some outcomes (primarily patient-reported outcomes and those related to rare events, as shown in Appendices 4 to 6), other outcomes had evidence rated as low to moderate and had effects large enough and estimated precisely enough to make recommendations for clinical practice.

In conclusion, ATT-PR improves exercise capacity, physical activity, self efficacy and probably quality of life. Its effects appear similar to conventional in/outpatient PR and equal or exceed those of home-based PR that does not use telehealth technology on quality of life, functional dyspnea and physical activity. High quality studies are still warranted to refine the uncertain estimates in this review and to provide data on cost-effectiveness.

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Figure legend

Figure 1. Study flow diagram.

Figure 2: Risk of bias among the included studies. Review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Short-term effect (1 to 4 months) of advanced telehealth technology to deliver PR on the 6MWT compared with (A) no PR, (B) in/outpatient PR and (C) home-based PR.

Figure 4. Short-term effect (1 to 4 months) of advanced telehealth technology to deliver PR on quality of life compared with (A) no PR, (B) in/outpatient PR using the SGRQ and (C) home-based PR.

Table 1: Characteristics of included studies

Advanced telehealth technology to deliver PR compared with no PR

First author (date)	Methods	Participants	Intervention	Outcomes	Notes
Demeyer (2017)	Multicenter RCT Data collection at 12 weeks for each intervention	343 patients with stable COPD who did not recently engage in PR (mean age 67 years, 64% males, mean FEV_1 56% predicted)	Intervention (12 weeks): usual care and telecoaching consisting in an initial motivational interview, booklet with in-home exercise, smartphone application and step counter (Fitbug Air) providing daily automated coaching through automatically weekly-adjusted activity goals (validated by investigators) and weekly message with tailored home activities. Follow up: telephone contact triggered in the case of non-compliance with wearing the step counter or technical problem Control: 5-10 min face to face discussion and standard leaflet explaining the importance of PA in COPD as well as information about PA recommendations and usual medical treatment	Objective physical activity (steps/day), time in moderate intense physical activity (MPA), walking time, movement intensity during walking, respiratory function, 6MWT, isometric quadriceps force, CAT, CCQ, mMRC, adverse event	About 5% of the patients experienced an AECOPD within the previous month
Moy (2015) and Moy (2016)	Monocentric RCT Data collection at 4 months (initial intensive phase) and 8 months thereafter (maintenance phase) for each intervention	239 sedentary veterans with COPD able to walk at least one block who can access and are able to use the internet (mean age 67 years, 94% males, unreported mean FEV_1 % predicted)	Intervention (12months): 4 months of intensive phase including website, daily use of a pedometer and weekly upload of step count, weekly automated individualised goals based on steps/day with motivational message, education support from the website and 8 months of maintenance phase (same program without any new educational content or motivational message). Follow-up: online community forum (social support)	SGRQ (total score and 3 dimensions), objective physical activity (steps/day), adverse event, AECOPD, emergency visit, mortality, study adherence	24% of the patients were long term oxygen users Outcomes are reported within two publications (initial intensive phase and maintenance phase)

			Control: no instruction to increase PA nor step-count goals; only wear the pedometer everyday and report their step-count and adverse event monthly.		1 participant with outlier data excluded
Nguyen (2013)	Three-arm multicenter RCT Data collection at 3, 6 and 12 months for each intervention	84 patients with stable COPD limited by dyspnea who maintained an SpO2 ≥ 85% on ≤ 6L/min of oxygen at the end of a 6MWT, who can access and are able to use the internet and did not recently engage in PR (mean age 69 years, 55% males, mean FEV_1 51% predicted)	Intervention (12 months): in-home dyspnea and exercise consultation (motivational interview), individualised exercise program (endurance: 30min, 4x/week of walking, cycling or swimming; upper limb strengthening: 3x/week) and adjusted according to the Borg scale, collaborative self- monitoring and reinforcement using technological enhanced support (personal computer/smartphone and a web-based tool to (1) upload real-time symptoms according to an individualised action plan for AECOPD management and received prompt feedback as well information/support, (2) upload exercise performed and (3) receive individualised goals settings by nurses), education and peer interaction (online modules and reinforcement with live chat sessions) Follow-up: biweekly personalised reinforcement and feedback using a web-based tool as well as real time alert to the nurse if worsening of symptoms Control group: home visit from one of the study staff, monthly face to face education sessions unrelated to lung disease and biweekly phone contact to provide general health information, without exercise	CRQ-D,6MWT, CPET (treadmill), BORG scale, arm endurance, CRQ, SF-36, self-efficacy, exercise behavior, perception of support, satisfaction	Three-arm study The results have been used for two different intervention:control analysis

Priori (2017)	Monocentric RCT Data collection at 2 months for each intervention	21 patients with COPD (mean age 69 years, unreported male/female ratio, mean FEV_1 44% predicted)	Intervention (2 months): automated coaching based on physical activity with weekly goals, daily feedback and coaching messages Control: no intervention	Objective physical activity (activity monitor providing A*ctive points*), utilisation	Available as an abstract only
Tabak (2014a)	Monocentric RCT Data collection at 1 month, 3 months, 6 months and 9 months for each intervention	29 patients with stable COPD who can access and are able to use the internet (mean age 63 years, 50% males, mean FEV_1 43% predicted)	Intervention (9 months): 4 modules : (1) activity coach for ambulant activity monitoring and real-time coaching of daily activity behavior (accelerometer and smartphone providing feedback, goals and motivational cues, (2) web-based individualised exercise program for home exercising (breathing exercise, resistance and endurance, airway clearance) using text support and videos and adapted online by a physiotherapist, (3) self-management of COPD exacerbations via a triage diary on the web portal, including self-treatment of exacerbations, and (4) teleconsultation. Follow-up: call to the study office if the patients desire assistance or consultation, teleconsultation Control: usual care, can attend physiotherapist regularly if prescribed as part of usual care	AECOPD, hospitalisations, length of stay, emergency department visit, objective physical activity (activity count via an accelerometer), subjective physical activity (Baecke Physical Activity Questionnaire), 6MWT, Multidimensional Fatigue Inventory 20, CCQ, mMRC, EuroQol-5D, evaluation of the online application (use of the application, adherence to the online diary, adherence to the exercise schemes, satisfaction (Client Satisfaction Questionnaire 8)	Some missing data at baseline
Tabak (2014b)	Pilot Monocentric RCT Data collection at 1, 2, 3 weeks for each intervention	34 patients with stable COPD without long-term oxygen therapy who can access and are able to use the	Intervention (4weeks): 2 out of the 4 modules from Tabak (2014a): (1) activity coach for ambulant activity registration and feedback and (minimum of 4 days/week), (2) web portal with a symptom diary for self-treatment of	Objective physical activity (steps/day), CCQ, mMRC, Multidimensional Fatigue Inventory 20, use of the system, compliance	

		internet and did not recently engage in PR (mean age 67 years, 63% males, mean FEV_1 53% predicted)	exacerbations and an overview of the measured activity levels Control group: usual care, can attend physiotherapist regularly if prescribed as part of usual care		
Tsai (2017)	Single-blind monocentric RCT Data collection at 8 weeks for each intervention	37 patients with COPD without long-term oxygen therapy who can access and are able to use the internet, can walk independently without a walking frame and did not recently engage in PR (mean age 74 years, 50% males, mean FEV_1 64% predicted)	Intervention (8 weeks): in-home visit with provision of equipment (laptop computer with in-built camera, cyclo ergometer and finger oximeter), real-time supervised/monitored group exercise training (3x/weeks) via desktop videoconferencing (Vsee) including cycling/walking (60-80% of the maximal capacity derived from the 6MWT and adjusted according to the BORG scale) and muscle strengthening (3x10 repetitions) Follow-up: real-time supervision of exercise session Control group: usual care without any exercise training	ESWT, 6MWT, ISWT, CRDQ, objective physical activity (energy expenditure, steps/day, metabolic equivalents), physical performance (FPI-SF), CAT, mMRC, HAD, self-efficacy (PRAISE), adverse event	

Advanced telehealth technology to deliver PR compared with in/outpatient PR

First author (date)	Methods	Participants	Intervention	Outcomes	Notes
Bourne (2017)	Monocentric single-blind RCT Data collection at 6 weeks for each intervention	90 patients with stable COPD and a mMRC dyspnea score ≥ 2 who can access and are able to use the internet, had no cognitive impairment	Intervention (6 weeks): access at least 5 times per weeks to myPR website (myMHealth) providing an online video-based exercise program (10 exercices of increasing duration over the 6 weeks) and educational videos: www. mymhealth. com/ mycopd	6MWT, CAT, SGRQ, HAD, adverse event	

		and did not recently engage in PR (mean age 70 years, 58% males, mean FEV_1 59% predicted)	Follow up: contact from the patient as necessary Control: 2 supervised outpatient session and 3 in-home unsupervised sessions per week. Exercises and educational content were similar to the experimental intervention but delivered face to face		
Chaplin (2017) and Barnes (2016)	Monocentric single-blind RCT Data collection at 6-7 weeks for each intervention	103 patients with COPD and a mMRC dyspnea score between 2 and 5 who can access and are able to use the internet and did not recently engage in PR (mean age 66 years, 69% males, mean FEV_1 57% predicted)	Intervention (6 to 8 weeks): introductory session about website access and navigation. The website provides an home exercise program and goal setting, a daily basis training including walking (speed: 85% baseline ISWT) and strength training both aimed to reach 4-7 on VAS for perceived exertion, an online exercise diary, an individual action plan for AECOPD management (based on the 'SPACE for COPD' manual) and an online educational program Follow-up: weekly online review and contact by a team member Control: 7 weeks separated in 4 weeks supervised and 3 weeks unsupervised. Supervised sessions occurred twice weekly and lasted 2 hours separated in 1 hour of exercise training and 1 hour of education session covering the same topics as the experimental intervention. Exercise included aerobic training (walking speed based on the baseline ISWT or cycling) and muscle strengthening (based on the 1RM) both adapted according to the BORG scale	Clinical outcomes: ISWT and ESWT, CRQ-SR; HADS, CAT, PRAISE, BCKQ, EQ-5D-5L, patient cost questionnaire, Euro-QOL, recruitment rate, completion rate, adverse event, physical activity (steps/hours, bouts of moderate activity for 2,5,10 and min/hours) Non-clinical outcomes: Web-usage audit for the internet-based programme, uptake and drop out	Data about PA were reported only as an abstract (Barnes 2016, ERS congress PA2056)

			(13-15). Patients were asked to complete home exercise for the remaining days		
Hansen (2020), Hansen (2019a) and Hansen (2019b)	Multicenter single-blind superiority RCT Data collection at the end of the intervention (3 months) for each intervention, at 3 months of follow-up and 1 year of follow-up	134 patients with severe to very severe COPD (mean age 68 years, 45% males, mean FEV_1 33% predicted)	Intervention (10 weeks): 60min, 3 times per weeks exercise sessions supervised by healthcare professional, including a 5min warm-up period, 30min of peripheral exercise muscle strengthening (4 sets of 8 to 25 repetitions at 40-80% of the 1RM adjusted according to the Borg scale), a 5min of cool-down period and 20min of self-management Control (12 weeks): conventional PR consisting in 60min, 2 times per weeks, supervised by healthcare professional exercise sessions including a 10min warm-up period, 30min of aerobic exercise training (cycling walking etc.), peripheral exercise muscle strengthening (2 to 3 sets of 8 to 25 repetitions at 40-80% of the 1RM), a 5-10min of cool-down period and 60 to 90min of self-management once per week.	6MWD, CAT, HAD, EQ-5D, CCQ, objective physical activity (accelerometer), 30sec-STS, hospitalisation rate, mortality, adverse event	

Advanced telehealth technology to deliver PR compared with home-based PR

First author (date)	Methods	Participants	Intervention	Outcomes	Notes
Dinesen (2012) and Haeseum (2012)	Monocentric RCT Data collection at 10 months for each intervention	111 patients with severe to very severe COPD (mean age 68 years, unreported male/female ratio,	Intervention (4 months of intervention and 6 months of follow-up): a web portal providing an in-home symptom and physiological data telemonitoring (BP, HR, weight, oxygen level, lung function) for early management of AECOPD and an exercise program (peripheral muscle	SF-36, hospitalisation rate for AECOPD, costs, QALY, ICER	

		unreported mean FEV_1 % predicted)	strengthening, stretching and walking with as step counter) Follow-up: health-care professionals can access the patient's data (including training inputs) and provide feedback through a web portal and monthly videoconferencing between health-care professionals to coordinate and discuss patients' individual rehabilitation program Control: patients were instructed on performing home exercises and made responsible for performing the activities by themselves without any formal planned contact		
Franke (2016)	Cross-over randomised study Data collection at 3 months for each intervention	44 stable COPD patients (mean age 63 years, unreported male/female ratio, mean FEV_1 48% predicted)	Intervention (3 months): home daily bicycle ergometer training (with exercise time telemonitored), intensity adjusted for the patient to be able to perform at least 30min of exercise (and subsequently self-adjusted) Follow-up: weekly phone call if mean exercise time per week is below 20min/day Home-based PR: same intervention without weekly phone call	Daily cycle exercise time, CAT, subjective physical activity (GLTEQ)	No evaluation of a carryover effect and unspecified washout period
Liu (2008)	Monocentric RCT Data collection every month during the first 3 months and at 1 year (9 months of follow-u))	48 patients with stable severe to very severe COPD but without long-term oxygen therapy	Intervention (3months): cell phone and application as a support to provide daily walking exercise training (intensity at 80% of the maximal capacity derived from the ISWT using an individualised music tempo as a feedback for the appropriate walking speed), booklet and	ISWT, SF-12, respiratory function, BMI, BORG, AECOD, hospitalisations, mortality, adherence	

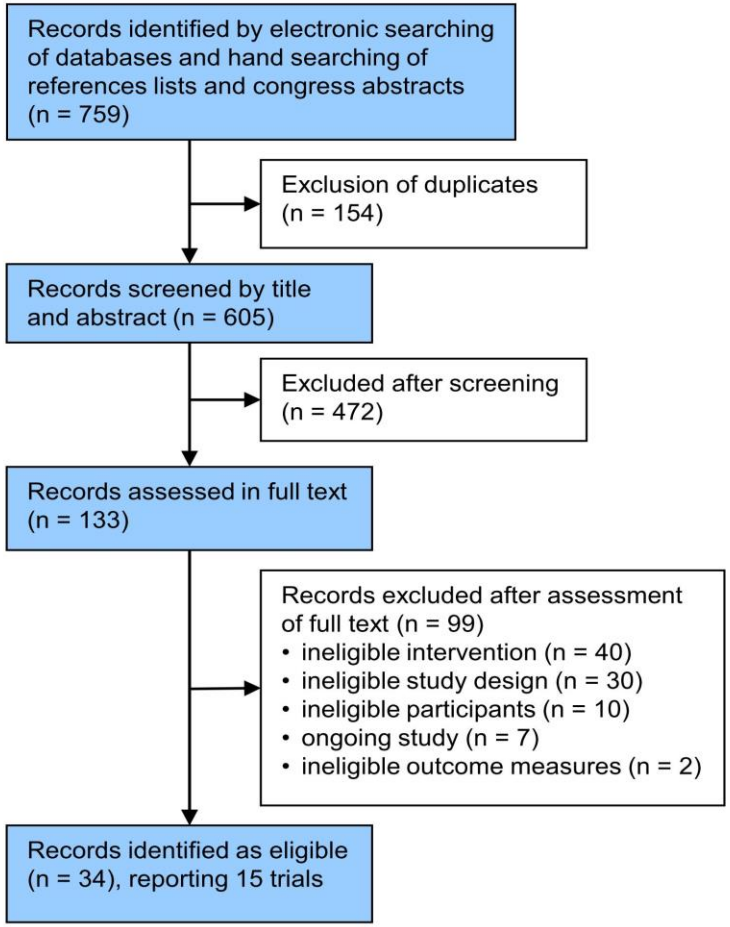
		(mean age 72 years, 100% males, mean FEV_1 46% predicted)	DVD providing instruction for home walking exercise Follow-up: training intensity adjusted during face to face visit in the clinic every 4 weeks during the first 3 months and every 3 months for the next 9 months, phone contact if walking training was missed for 1 day Control: home-based PR consisting in the same protocol (without music tempo for walking training) with phone follow-up every 2 weeks during the first 3 months		
Nguyen (2008)	Multicenter RCT Data collection at 3 and 6 months for each intervention	50 patients with stable COPD limited by dyspnea who maintained an SpO2 ≥ 85% on ≤ 6L/min of oxygen at the end of a 6MWT, who can access and are able to use the internet and did not recently engage in PR (mean age 70 years, 56% males, mean FEV_1 50% predicted)	Intervention (6 months): see Nguyen (2013) The initial consultation was performed in the center and a smartphone was provided by investigators Control: same intervention than the experimental intervention but: symptoms and exercise performed are monitored through paper diaries send to the centre; and education was provided through paper support and reinforcement performed face to face Follow-up: phone call instead of the web-based tool and no real-time alert to the nurse if worsening of symptoms The initial consultation was performed in the center	CRQ-D, exercise behavior, 6MWT, CRQ, SF-36, COPD knowledge, self-efficacy, perception of support, preference, satisfaction	The investigators stopped the study early due to the cumulative technical and usability challenges that peaked when three consecutive participants in the intervention group had multiple difficulties accessing the Web application and subsequently withdrew

Nguyen (2013)	Three-arm multicenter RCT Data collection at 3, 6 and 12 months for each intervention	84 patients with stable COPD limited by dyspnea who maintained an SpO2 ≥ 85% on ≤ 6L/min of oxygen at the end of a 6MWT, who can access and are able to use the internet and did not recently engage in PR (mean age 69 years, 55% males, mean FEV_1 51% predicted)	Intervention (12 months): in-home dyspnea and exercise consultation (motivational interview), individualised exercise program (endurance: 30min, 4x/week of walking, cycling or swimming; upper limb strengthening: 3x/week) and adjusted according to the Borg scale, collaborative self- monitoring and reinforcement using technological enhanced support (personal computer/smartphone and a web-based tool to (1) upload real-time symptoms according to an individualised action plan for AECOPD management and received prompt feedback as well information/support, (2) upload exercise performed and (3) receive individualised goals settings by nurses), education and peer interaction (online modules and reinforcement with live chat sessions) Follow-up: biweekly personalised reinforcement and feedback using a web-based tool as well as real time alert to the nurse if worsening of symptoms Control: the same intervention than the experimental intervention but (1) symptoms and exercise performed are monitored through paper diaries send to the center and (2) education was provided through paper support and reinforcement performed face to face Follow-up: phone call instead of the web-based tool and no real-time alert to the nurse if worsening of symptoms	CRQ-D, 6MWT, CPET (treadmill), BORG scale, arm endurance, CRQ, SF-36, self-efficacy, exercise behavior, perception of support, satisfaction	Three-arm study The results have been used for two different intervention:control analysis Exercise interventions are unsupervised for the two groups without any difference on that component between groups. The principal differences between the two programs lies on the dyspnea management component

Wan (2017) and Robinson (2019)	Single-blind monocentric RCT Data collection at 3 months for each intervention	114 veterans with stable COPD able to walk at least one block and dot not desaturate < 85% SpO2 during the 6MST, who can access and are able to use the internet and did not recently engage in PR (mean age 69 years, 98% males, mean FEV_1 62,6% predicted)	Intervention (3 months): daily pedometer wearing, weekly update of the step-count, access to a website providing weekly automated individualised goals settings, interactive step-count feedback, education/motivational content for self-management and self-efficacy) and online community forum (social support) Follow-up: online community support (no further information provided) Control: daily pedometer use, monthly update of the step count, written materials about exercise but no step-count goals and no information provided on the website	Objective physical activity (steps/day), 6MWT, exercise adherence, respiratory function, SGRQ, mMRC, Beck Depression Inventory, Bristol COPD Knowledge Questionnaire, Exercise Self-Regulatory Efficacy Scale, Medical Outcome Study Social Support Survey, adverse event, AECOPD, self-reported physical health	Robinson (2019) is a secondary analysis of Wan (2017) with a slightly different number of participants (n=112) The results are therefore different in the two studies (at least for self-efficacy, steps per day and the 6MWT)

PR: pulmonary rehabilitation, **RCT**: randomised controlled trial, **COPD**: chronic obstructive pulmonary disease, **FEV1 :** forced expiratory volume in one second, **PA**: physical activity, **MPA**: Moderate Physical Activity, **6MWT**: six-minute walk test, **CAT**: COPD assessment test, **CCQ**: clinical COPD questionnaire, **mMRC**: modified Mediral Research Council dyspnea score, **AECOPD**: acute exacerbation of chronic obstructive pulmonary disease, **SGRQ**: St George's Respiratory Questionnaire, **eDSMP**: internet-based dyspnea self-management program, **CRQ-D**: chronic respiratory questionnaire dyspnea subscale, **CPET**: incremental cardiopulmonary exercise testing, **CRQ**: chronic respiratory questionnaire, **SF-36**: Short Form Health Survey, **CCQ**: Clinical COPD Questionnaire, **EQ-5D**: EuroQol-5 dimensions, **BMI**: body mass index, **ESWT**: endurance shuttle walk walkking exercise test, **ISWT**: incremental shuttle walking exerice test, **CRDQ**: Chronic Respiratory Disease Questionnaire, **FPI-SF**: Performance Inventory – Short Form, **HAD**: anxiety and depression scale, **PRAISE**: Pulmonary Rehabilitation Adapted Index of Self-Efficacy, **VAS**: visual analogue scale, **1RM**: one repetition maximum, **CRQ-SR**: chronic respiratory questionnaire, self reported, **BCKQ**: Bristol COPD knowledge questionnaire, **QOL**: quality of life, **ERS**: European Respiratory Congress, STS: Sit To Stand, **ATS**: American Thoracic Society, **BP**: blood pressure, **HR**: heart rate, **QALY**: quality-adjusted life years, **ICER**: incremental cost-effectiveness ratio, **SF-12**: Short Form-12 quality of life questionnaire, **GLTEQ**: Godin Leisure Time Exercise Questionnaire, **SpO2**: pulsed oxygen saturation, **fDSMP**: face to face dyspnea self-management program, **6MST**: 6 minute stepper test.

Figure 1


Records identified by electronic searching of databases and hand searching of references lists and congress abstracts (n = 759)
Exclusion of duplicates (n = 154)
Records screened by title and abstract (n = 605)
Excluded after screening (n = 472)
Records assessed in full text (n = 133)
Records excluded after assessment of full text (n = 99)
• ineligible intervention (n = 40)
• ineligible study design (n = 30)
• ineligible participants (n = 10)
• ongoing study (n = 7)
• ineligible outcome measures (n = 2)
Records identified as eligible (n = 34), reporting 15 trials

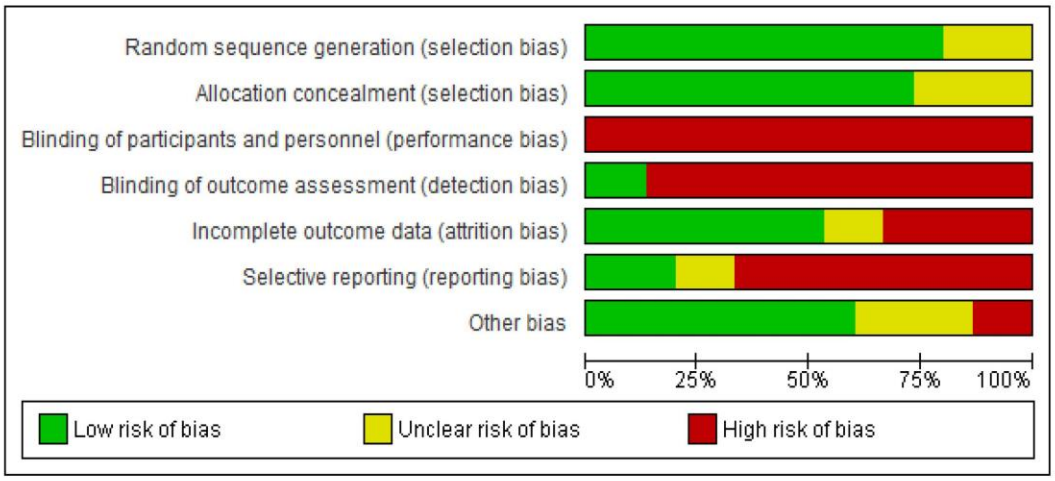
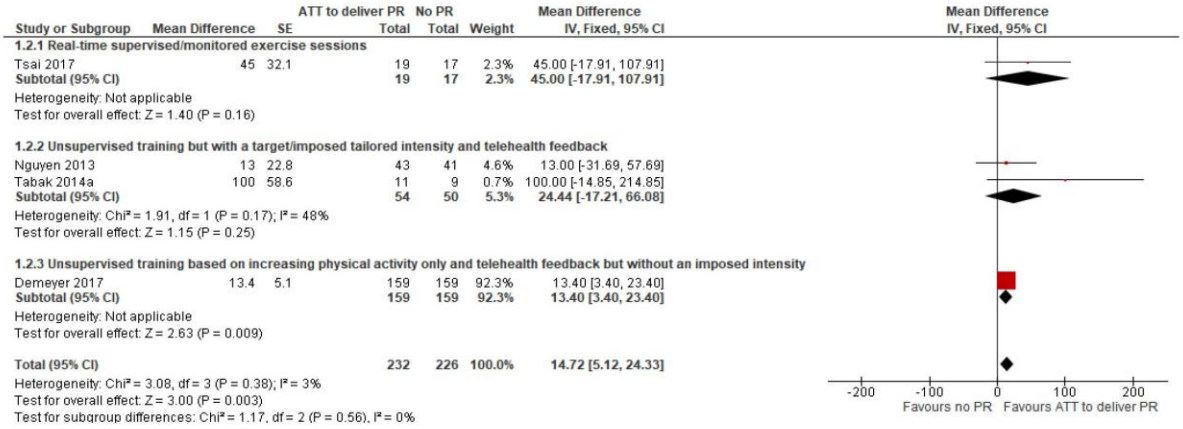


Figure 2. Risk of bias among the included studies. Review authors' judgements about each risk of bias item presented as percentages across all included studies. For individual study scores, see Appendix 3 on the eAddenda.

A



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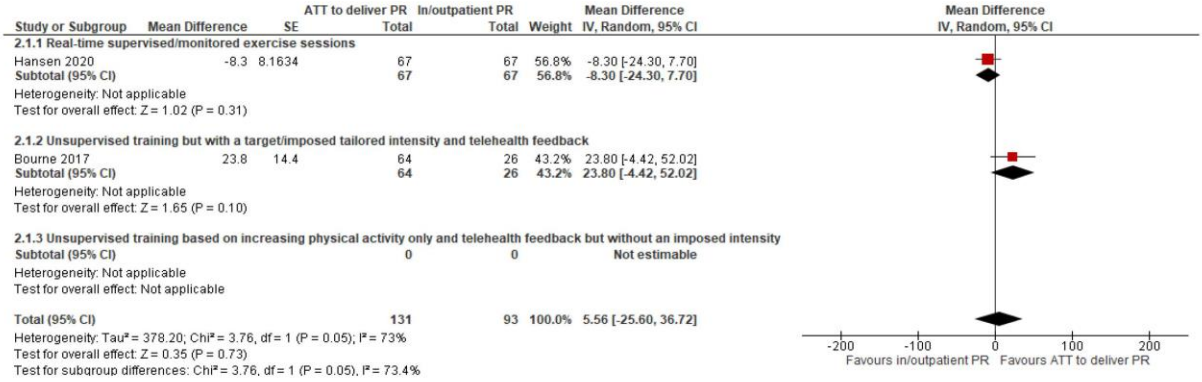

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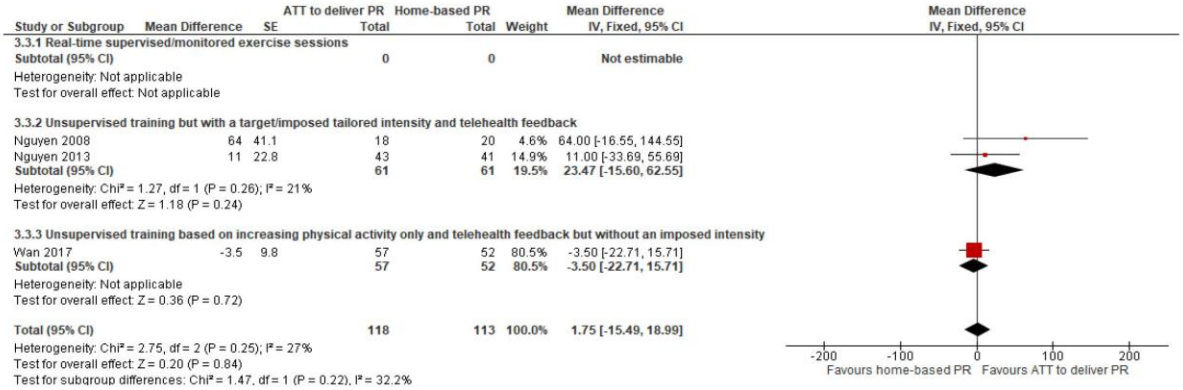
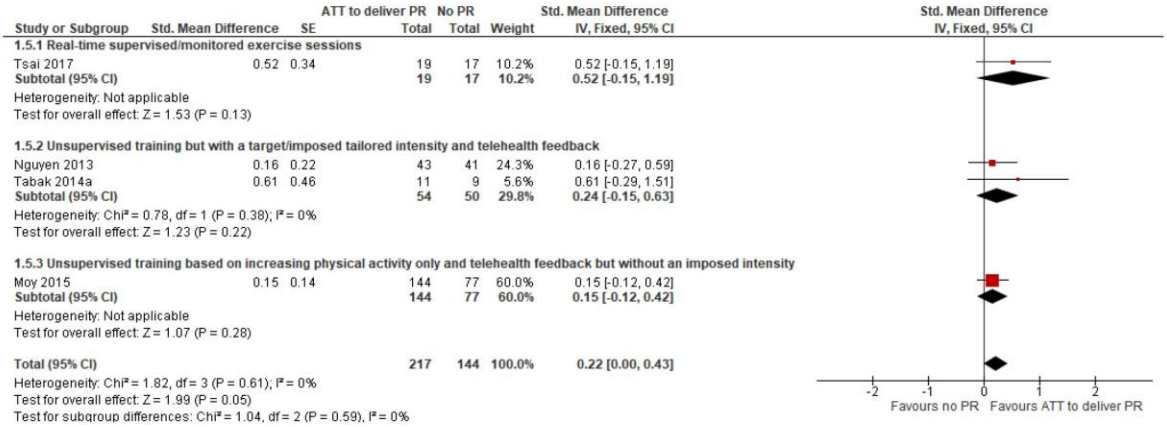


Figure 3. Short-term effect (1 to 4 months) of advanced telehealth technology to deliver PR on the 6MWT compared with (A) no PR, (B) in/outpatient PR and (C) home-based PR.

ATT: advanced telehealth technology, **PR:** pulmonary rehabilitation, **6MWT**: six-minute walk test.

A



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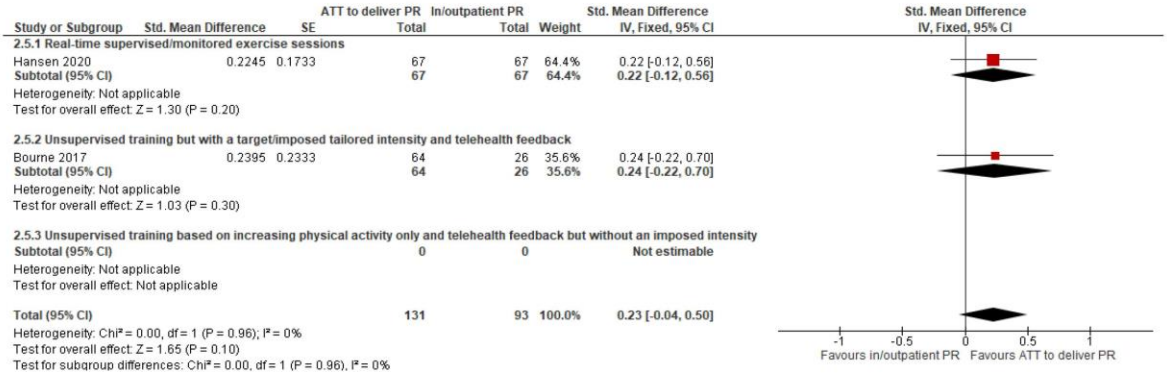

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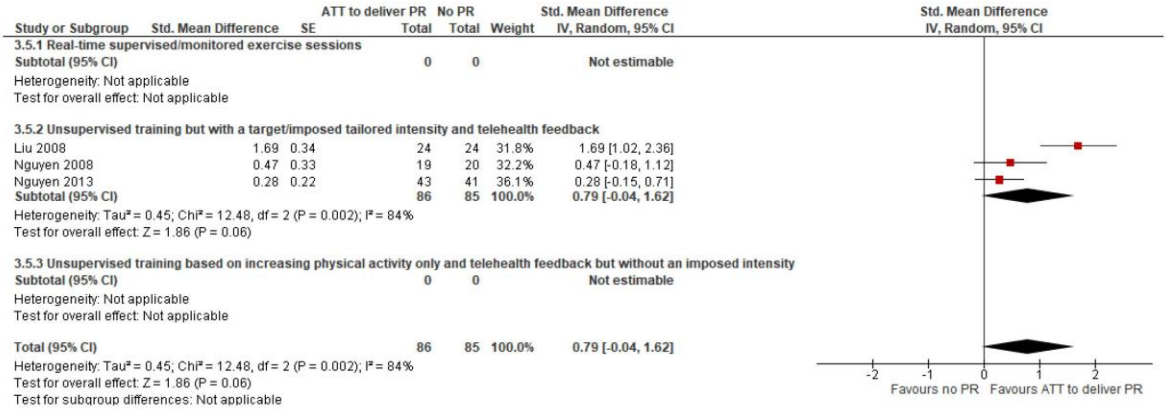

Figure 4. Short-term effect (1 to 4 months) of advanced telehealth technology to deliver PR on quality of life compared with (A) no PR, (B) in/outpatient PR using the SGRQ and (C) home-based PR.

ATT: advanced telehealth technology, **PR:** pulmonary rehabilitation, **SGRQ**: St George's Respiratory Questionnaire

Dear Ms Burbery,

We are pleased to submit our manuscript "Advanced telehealth technology improves in-home pulmonary rehabilitation for people with stable chronic obstructive pulmonary disease: a systematic review" for consideration for publication in *Journal of Physiotherapy*. As the journal's editor, Mark Elkins, is an author on this manuscript, we ask that you invite one of the other Editorial Board members to take on the role of the guest editor in this instance.

The manuscript reports a systematic review in the area of home-based pulmonary rehabilitation. While a large body of evidence supports the effectiveness of pulmonary rehabilitation, it arguably should be offered to as many people as possible. Actually, as little as 5% of those people who would benefit from it actually engage in such a program. Advanced telehealth technology pulmonary rehabilitation (ATT-PR; describing the delivery of in-home PR using any more advanced telehealth technology than phone contact or pedometer alone) may address this issue by increasing the supply of pulmonary rehabilitation while enabling the same peer-support than centre based pulmonary rehabilitation provides. The systematic review answers three important clinical questions about ATT-PR, which are: how effective is ATT-PR for people with COPD, compared with no PR; how effective is ATT-PR for people with COPD, compared with in/outpatient PR; and how effective is ATT-PR for people with COPD, compared with home-based PR not using such technologies? Using a thorough search strategy, duplicate data processes and minimal language bias, the systematic review provides large and precisely enough estimates of the effects of ATT-PR related to these three questions to make recommendations for clinical practice.

The study was prospectively registered. Possible reviewers are listed below. If you have any questions or if anything seems incomplete or not in order, please do not hesitate to contact myself or Mark for clarification.

Thank you for your consideration of our manuscript.
Yours sincerely,
Tristan Bonnevie

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Dr Catherine Johnston, University of Newcastle - cath.johnston@newcastle.edu.au
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Appendix 1. Example search strategy.

The search strategy for PubMed, shown below, used a sensitivity-maximising searching method. It was adapted for the other databases.

#1 "COPD"[tiab] OR "pulmonary disease, chronic obstructive"[mh] OR "lung diseases, obstructive"[mh] OR "chronic obstructive pulmonary disease"[tiab] OR "chronic respiratory failure"[tiab] OR "obstructive airway"[tiab] OR "bronchitis, chronic"[mh] OR "pulmonary disease"[tiab] OR "emphysema"[tiab] OR "emphysema"[mh]

#2 "telehealth"[tiab] OR "telemedicine"[tiab] OR "telemedicine"[mh] OR "telecare"[tiab] OR "telehomecare"[tiab] OR "videoconferencing"[tiab] OR "videoconferencing"[mh] OR "ehealth"[tiab] OR "real-time"[tiab] OR "health technology"[tiab] OR "biomedical technology"[tiab] OR "biomedical technology"[mh] OR "home care services"[tiab] OR "home care services"[mh] OR "web-based"[tiab] OR "phone-based"[tiab] OR "internet-based"[tiab]

#3 "exercise"[tiab] OR "exercise"[mh] OR "rehabilitation"[tiab] OR "rehabilitation"[mh] OR "pulmonary rehabilitation"[tiab] OR "physical activity"[tiab] OR "activity, physical"[mh] OR "training"[tiab] OR "walking"[tiab] OR "walking"[mh] OR "physical fitness"[tiab] OR "physical fitness"[mh]

#4 "telerehabilitation"[tiab] OR "telerehabilitation"[mh]

#5 "randomized controlled trial"[pt] OR "randomized controlled trial"[tiab] OR "controlled clinical trial"[pt] OR "controlled clinical trial"[tiab] OR "randomized"[pt] OR "randomized"[tiab] OR "random"[pt] OR "random"[tiab]

#6 #1 AND #2 AND #3

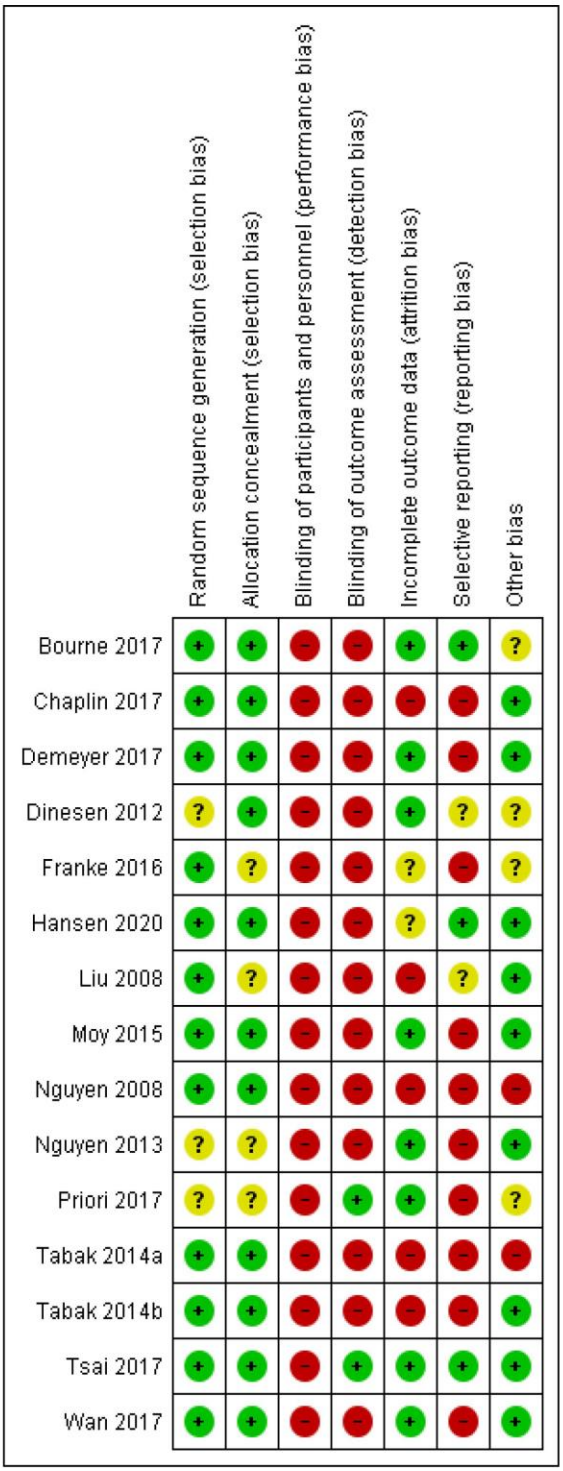
#7 #1 AND #4

#8 #6 OR #7 AND #5

[tiab] = a word in the title or abstract, [mh] = a Medical Subject Heading term, [pt] = a Publication Type term.

Appendix 2. Risk of bias summary.

Review authors' judgements about each risk of bias item for each included study.



Appendix 3. Detailed evaluation of the risk of bias.

Detailed evaluation of the risk of bias among the studies where pulmonary rehabilitation delivered using advanced telehealth technology was compared with no pulmonary rehabilitation.

Risk of bias – Demeyer et al. 2017		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"The random sequence was generated with varying block sizes of 4, 6 or 8 and stratified by centre using a statistical software (STATA V.12.0, StataCorp, College Station, Texas, USA)"
Allocation concealment (selection bias)	Low	"[…] investigators obtained group allocation using an online system that ensured concealment of random allocation"
Blinding : participant and personnel (performance bias)	High	"Lastly, neither patients nor investigators were blinded to treatment allocation"
Blinding : outcome assessment (detection bias)	High	The author's judgement of observer-reported outcomes involving some judgement and patient-reported outcomes is « High » (see above) The primary outcome (objective physical activity measurement) can be considered as an observer-reported outcomes not involving judgement and is unlikely to be influenced by the lack of blinding of investigators The author's judgement of this outcome is « Low »
Incomplete outcome data (attrition bias)	Low	Dropout rate inferior to 15% and equally distributed among groups (flowchart)
Selective reporting (reporting bias)	High	Clinically relevant outcomes announced in the NCT registration are not reported (HAD and mMRC scores)
Other	Low	No competing interests related with the study and comparable baseline characteristics "Competing interests: none declared" "Baseline characteristics were comparable between groups with regard to factors influencing PA"

Risk of bias – Moy et al. (2015) and Moy et al. (2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"Group assignment was computer generated, and randomization was stratified by dyspnea and urban vs rural residence"
Allocation concealment (selection bias)	Low	See above
Blinding : participant and personnel (performance bias)	High	No information provided but patients were informed about the study design and the control group consisted in those patients on the waiting list
Blinding : outcome assessment (detection bias)	High	No information provided The author's judgement of patient-reported outcome is « High » (see above) There was not observer-reported outcomes involving some judgement Some secondary outcomes (objective physical activity measurement, AECOPD and mortality) can be considered as observer-reported outcomes not involving judgement and are unlikely to be influenced by the lack of blinding of investigators The author's judgement of these outcomes is « Low »
Incomplete outcome data (attrition bias)	Low	"The final analysis used the intent-to-treat approach" but results at 4 months are shown only for completers Low attrition rate (about 5%), evenly distributed among groups
Selective reporting (reporting bias)	High	Main outcomes were specified in the NCT registration but some unspecified outcomes appear in the manuscripts (AECOPD and hospitalization rates) Change in the mMRC dyspnea score was specified in the NCT registration but is lacking in the manuscripts
Other	Low	No competing interests related with the study and comparable baseline characteristics "There were no significant differences in baseline characteristics between study groups" "Financial/nonfinancial disclosures: The authors have reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article"

Risk of bias – Nguyen et al. (2013)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	"We conducted a randomized, repeated measures (0, 3, 6, 12 months) study to test the efficacy of two 12-month DSMPs, eDSMP and fDSMP, compared with GHE" No more information about method to generate the random sequence
Allocation concealment (selection bias)	Unclear	No information provided
Blinding : participant and personnel (performance bias)	High	No information provided but the blinding of participants seems not feasible in the context of the study design
Blinding : outcome assessment (detection bias)	High	The author's judgement of patient-reported outcome is « High » (see above) Assessment staff was not involved in the intervention, but no information is provided about its awareness of the group allocation. Therefore, the author's judgement of observer-reported outcomes involving some judgement is « Unclear » "Participants returned to the medical center at three, six, and 12 months for testing by study staff who were not involved in the intervention" There was no observer reported outcome not involving judgement
Incomplete outcome data (attrition bias)	Low	"We incorporated intent-to-treat principles whereby participants were analyzed according to their group assignment regardless of their adherence with the treatment and subsequent withdrawal" 15 patients (12%) withdrew from the study and were evenly distributed among groups
Selective reporting (reporting bias)	High	Some negative secondary outcomes are not reported with sufficient details but the p value is provided. "There were no differences among the groups on the change in performance on the treadmill test or on dyspnea intensity rated on the Borg Scale during the 6MWT and ITT
		"Participants were similar at baseline across all groups" "The authors declare no conflicts of interest"

Risk of bias – Priori et al. (2017)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	"patient were randomized to the intervention (IG) or control (CG) group for 2 months" No more information about method to generate the random sequence
Allocation concealment (selection bias)	Unclear	No information provided
Blinding : participant and personnel (performance bias)	High	No information provided but the blinding of participants seems not feasible in the context of the study design
Blinding : outcome assessment (detection bias)	Low	The only outcome reported (objective physical activity) can be considered as an observer-reported outcomes not involving judgement and is unlikely to be influenced by the lack of blinding of investigators
Incomplete outcome data (attrition bias)	Low	3 patients (14%) withdrew from the study
Selective reporting (reporting bias)	High	No study registration provided Only one outcome reported
Other	Unclear	"baseline PA" was comparable in the two groups but the comparison of other important baseline demographic data between groups is lacking No statement of conflict of interests

Risk of bias – Tabak et al. (2014a)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"Patients were randomized using a computer-generated randomization list (Blocked Stratified Randomization version 5; Steven Piantadosi), where randomization was applied in random blocks of two and four"
Allocation concealment (selection bias)	Low	"Participants were allocated by a data manager in order of inclusion following the randomization list, placed in a sealed envelope"
Blinding : participant and personnel (performance bias)	High	No information provided but the blinding of participants seems not feasible in the context of the study design
Blinding : outcome assessment (detection bias)	High	No information provided The author's judgement of patient-reported outcome is « High » (see above) The author's judgement of observer-reported outcomes involving some judgement is « Unclear » Some secondary outcomes (objective physical activity measurement, AECOPD, hospitalizations) can be considered as observer-reported outcomes not involving judgement and are unlikely to be influenced by the lack of blinding of investigators. The author's judgement of these secondary outcomes is « Low »
Incomplete outcome data (attrition bias)	High	"To present the outcome measures over time in both groups, a mixed-model analysis for repeated measures was performed (intention to treat)" 17 patients withdrew (59%) and were not equally distributed among groups (33% and 86% for the intervention group and the control group respectively)
Selective reporting (reporting bias)	High	Outcomes in accordance with the study registration but clinical outcomes were performed at 1, 3, 6 and 9 months but are only presented at 1 and 3 months without p value
Other	High	No competing interests related with the study but differences in baseline characteristics "There was a significant difference found for baseline dyspnea levels between groups (P=0.03), showing better clinical measures in the telehealth group" "The authors report no conflicts of interest in this work"

Risk of bias – Tabak et al. (2014b)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"Eligible participants were randomly assigned to either the intervention or control group according to a computer-generated randomization list"
Allocation concealment (selection bias)	Low	"Recruitment, randomization, and allocation were performed by different persons"
Blinding : participant and personnel (performance bias)	High	No information provided but the blinding of participants seems not feasible in the context of the study design
Blinding : outcome assessment (detection bias)	High	No information provided The author's judgement of patient-reported outcome is « High » (see above) There was no observer-reported outcomes involving some judgement The primary outcome (objective physical activity measurement) can be considered as an observer-reported outcome not involving judgement and is unlikely to be influenced by the lack of blinding of investigators. The author's judgement of this outcome is « Low »
Incomplete outcome data (attrition bias)	High	4 patients (12%) withdrew from the study but were all in the intervention group
Selective reporting (reporting bias)	High	Some outcomes reported were not specified in the Netherlands Clinical Trial Register registration (health status, dyspnea, fatigue)
Other	Low	No competing interests related with the study and comparable baseline characteristics "The intervention and control group were similar in age, gender, lung function, smoke status, dyspnoea level, body mass index, and employment status (all $p > 0.05$) (Table 1)" "The author declares that there is no conflict of interest"

Risk of bias – Tsai et al. (2017)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"Participants were randomized by one of the investigators (L.L.Y.T.) using a computer generated sequence […] and concealed allocation to one of the two groups"
Allocation concealment (selection bias)	Low	See above
Blinding : participant and personnel (performance bias)	High	"This study was a prospective, blinded (assessor and statistician) RCT"
Blinding : outcome assessment (detection bias)	Low	The author's judgement of patient-reported outcome is « High » (see above) The author's judgement of observer-reported outcomes involving some judgement and observer-reported outcome not involving judgement is « Low » (see above)
Incomplete outcome data (attrition bias)	Low	"Intention-to-treat analysis was conducted with no imputation of missing values" 1 patient (3%) withdrew from the study
Selective reporting (reporting bias)	Low	Outcomes specified in the method section are present in the results section and are in accordance with those specified in the study registration Qualitative outcome are reported in a different manuscript
Other	Low	No competing interests related with the study and comparable baseline characteristics "Baseline characteristics were similar between the two groups" "This study was financially supported by the NSW Agency for Clinical Innovation (ACI), NSW, Australia, and South Eastern Local Health District Chronic Care Service Redesign Grant, NSW, Australia"

Detailed evaluation of the risk of bias among the studies where pulmonary rehabilitation delivered using advanced telehealth technology was compared with in/outpatient PR.

Risk of bias – Bourne et al. (2017)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"We randomised eligible patients with COPD using a computerised block permutation randomise sequencer in a ratio of 2:1 to either the online arm (myPR) or to receive standard face-to-face PR"
Allocation concealment (selection bias)	Low	"Randomisation was stratified by severity of COPD (forced expiratory volume in 1 s (FEV1)% predicted) to ensure equal distribution in both arms and used an online system for concealed allocation"
Blinding : participant and personnel (performance bias)	High	"Due to the nature of the intervention, blinding of participants was not possible" There was no observer-reported outcome not involving judgement
Blinding : outcome assessment (detection bias)	High	The author's judgement of patient-reported outcome is « High » (see above) The author's judgement of observer-reported outcomes involving some judgement is « Low » (see above) "Study staff carrying out the postintervention assessments (outcome assessors) were blind to which arm the patient had been randomised to" There was no observer-reported outcome not involving judgement
Incomplete outcome data (attrition bias)	Low	"Statistical analysis was performed for both the intention-to-treat (ITT) population and per-protocol (PP) population. ITT analysis included all participants in the arms they were randomised to regardless of adherence to either intervention"
Selective reporting (reporting bias)	Low	Important outcomes reported All outcomes announced in the NCT registration are reported
Other	Unclear	Some authors report competing interest with myMHealth: "Dr Bourne reports grants and personal fees from myMHealth […]. He is CEO, co-founder and part owner of this company (a medical software company); Mrs De Vos reports personal fees from myMHealth; Dr Green reports grants to Portsmouth Hospitals NHS Trust from myMHealth, during the conduct of the study; Dr Cornelius reports personal fees from myMHealth,

	during the conduct of the study; Dr Brown reports grants from myMHealth, during the conduct of the study; Professor Wilkinson reports grants and personal fees from myMHealth during the conduct of the study. He is co-founder and part owner of this company" Similar baseline characteristics "No important imbalances were identified for these variables between the two intervention groups"

Risk of bias – Chaplin et al. (2017) and Barnes (2016)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"Patients were randomised to either the conventional rehabilitation programme as is standard at their referred site or the web-based PR programme (SPACE for COPD). Randomisation to the treatment group allocation was on a 1:1 ratio to either group and was performed using a web-based programme (http://www.sealedenvelope.com)."
Allocation concealment (selection bias)	Low	"Randomisation to the treatment group allocation was on a 1:1 ratio to either group and was performed using a web-based programme (http://www.sealedenvelope.com)"
Blinding : participant and personnel (performance bias)	High	"Figure 5: Patient preference for programme setting prior to randomization"
Blinding : outcome assessment (detection bias)	High	The author's judgement of patient-reported outcome is « High » (see above) The author's judgement of observer-reported outcomes involving some judgement and the author's judgement of observer-reported outcomes not involving judgement is « Low » "Clinical measures were performed at baseline and repeated again at the discharge assessment following completion of either rehabilitation programme (usually ~6–7 weeks after starting the programme) and were conducted by a research physiotherapist who was blinded to treatment group allocation"
Incomplete outcome data (attrition bias)	High	No intention to treat analysis and 41 patients (40%) withdrew Droup out (n=29/51) in the web-based group (attrition = 57%).
Selective reporting (reporting bias)	High	Only two clinical outcomes reported among those specified in the method section "There were no significant differences between the groups in any clinical outcome" Outcomes announced in trial registration not all reported (ISRCTN03142263) Protocol published (Chaplin et al. BMJ Open 2015)
Other	Low	No competing interests related with the study and comparable baseline characteristics "Competing interests: none declared"

Risk of bias – Franke et al. (2017)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"The consenting patients were randomized to the study using a previously created randomization list"
Allocation concealment (selection bias)	Unclear	No information provided
Blinding : participant and personnel (performance bias)	High	No information provided but the blinding of participants seems not feasible in the context of the study design
Blinding : outcome assessment (detection bias)	High	The author's judgement of observer-reported outcomes involving some judgement and patient-reported outcomes is « High » (see above) There was no observer-reported outcomes involving some judgement The primary outcome (daily cycle exercise time) can be considered as an observer-reported outcomes not involving judgement and is unlikely to be influenced by the lack of blinding of investigators. The author's judgement of this secondary outcomes is « Low »
Incomplete outcome data (attrition bias)	Unclear	9 patients (17%) withdrew the study without period specification for 4 of them
Selective reporting (reporting bias)	High	The BODE index was specified in the ClinicalTrials registration but does not appear in the manuscript Subjective measurement of physical activity was not specified in the ClinicalTrials registration but is present in the manuscript
Other	Unclear	Non specified washout period and no assessment of a carry-over effect (cross-over study) which may impact primary outcome (any habits in exercise training following intervention may be maintained during the controlled intervention) No competing interests related with the study "Karl-Josef Franke, Ulrike Domanski, Maik Schroeder, Volker Jansen, Frank Artmann, Uwe Weber, Rainer Ettler and Georg Nilius declare that they have no financial involvement in the subject discussed in the submitted manuscript and that there are no conflicts of interest in this work" No information are provided about differences between groups at baseline

Risk of bias – Liu et al. (2008)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"Initially, 60 patients were enrolled and 30 were assigned to the cell phone group according to a table of random numbers"
Allocation concealment (selection bias)	Unclear	No information provided
Blinding : participant and personnel (performance bias)	High	No information provided but the blinding of participants seems not feasible in the context of the study design
Blinding : outcome assessment (detection bias)	High	No information provided The author's judgement of patient-reported outcomes is « High » (see above) The author's judgement of of observer-reported outcomes involving some judgement is « Unclear » Other secondary outcomes (AECOPD, hospitalization and mortality) can be considered as observer-reported outcomes not involving judgement and are unlikely to be influenced by the lack of blinding of investigators. The author's judgement of these secondary outcomes is « Low »
Incomplete outcome data (attrition bias)	High	Per protocol analyze and 12 patients (20%) withdrew from the study including 4 in the intervention group due to difficulty in operating the cell phone
Selective reporting (reporting bias)	Unclear	No study registration provided Main specified outcomes in the method section are reported in the results section
Other	Low	No competing interests related with the study and comparable baseline characteristics "There were no significant differences between the two groups in terms of age, sex, BMI, initial exercise capacity, severity of COPD, pulmonary function or the extent of dynamic hyperinflation. There were no significant differences in either the maintenance medications or in the baseline SF-12 scores" "Statement of interest: none declared"

Risk of bias – Nguyen et al. (2008)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"An investigator who was not involved in the day-to-day study operations generated the randomization sequence using the SPSS version 14.0 (SPSS Inc, Chicago, IL, USA) random sequence generator feature and placed the randomization in separate sealed opaque envelopes"
Allocation concealment (selection bias)	Low	See above
Blinding : participant and personnel (performance bias)	High	"Approximately 66% of the sample expressed a preference for one of the two dyspnea self-management programs" "participants were not informed of their assignment until the visit was complete"
Blinding : outcome assessment (detection bias)	High	The author's judgement of patient-reported outcome is « High » (see above) Assessment staff was not involved in the intervention, but no information is provided about its awareness of the group allocation. Therefore, the author's judgement of observer-reported outcomes involving some judgement is « Unclear » "They returned to the medical center at 3 and 6 months for testing by study staff who were not involved in the intervention. Individual semistructured interviews were conducted either in person or via telephone at the final visit by the evaluation staff or investigators (HQN and VCK) who were not directly involved in the intervention" There was no observer reported outcome not involving judgement
Incomplete outcome data (attrition bias)	High	"We incorporated intent-to-treat principles" but 11 patients (22%) withdrew (evenly distributed among groups) and "those who dropped out tended" or had significant different demographic characteristics than those who did not "The investigators stopped the study early due to the cumulative technical and usability challenges that peaked when three consecutive eDSMP participants had multiple difficulties accessing the Web application and subsequently withdrew" In addition, results are reported for completers
Selective reporting (reporting bias)	High	Outcomes specified in the method section are reported in the result section but some were not

		specified in the NCT registration (tool used to assess dyspnea, SF-36, 6MWT)
Other	High	No competing interests related with the study and comparable baseline characteristics "Participants in both treatment groups were similar on all baseline characteristics" "Conflicts of Interest: None declared" Study stopped prematurely "Due to the technical and usability challenges with the Web and PDA application and differential participant attrition, we terminated the study before reaching our sample target"

Risk of bias – Nguyen et al. (2013)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	"We conducted a randomized, repeated measures (0, 3, 6, 12 months) study to test the efficacy of two 12-month DSMPs, eDSMP and fDSMP, compared with GHE" No more information about method to generate the random sequence
Allocation concealment (selection bias)	Unclear	No information provided
Blinding : participant and personnel (performance bias)	High	No information provided but the blinding of participants seems not feasible in the context of the study design
Blinding : outcome assessment (detection bias)	High	The author's judgement of patient-reported outcome is « High » (see above) Assessment staff was not involved in the intervention, but no information is provided about its awareness of the group allocation. Therefore, the author's judgement of observer-reported outcomes involving some judgement is « Unclear » "Participants returned to the medical center at three, six, and 12 months for testing by study staff who were not involved in the intervention" There was no observer-reported outcome not involving judgement
Incomplete outcome data (attrition bias)	Low	"We incorporated intent-to-treat principles whereby participants were analyzed according to their group assignment regardless of their adherence with the treatment and subsequent withdrawal" 15 patients (12%) withdrew from the study and were evenly distributed among groups
Selective reporting (reporting bias)	High	Some negative secondary outcomes are not reported with sufficient details but the p value is provided. "There were no differences among the groups on the change in performance on the treadmill test or on dyspnea intensity rated on the Borg Scale during the 6MWT and ITT (P>0.05)" Some important outcome specified in the NCT registration are not reported in the manuscript (AECOPD, health resource utilization)
Other	Low	No competing interests related with the study and comparable baseline characteristics

	“Participants were similar at baseline across all groups”
	“The authors declare no conflicts of interest”

Risk of bias – Wan (2017) and Robinson et al. (2019)		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	"Subjects were then randomized (1:1) by a computer algorithm [23] with blocking stratified on season and baseline 6-minute walk test (6MWT) distance (dichotomized by ≥ 1190 feet or < 1190) to either pedometer plus website (intervention) or pedometer alone (control) groups"
Allocation concealment (selection bias)	Low	"Randomization assignments were generated with random block sizes which were not disclosed to study staff. Assignments were communicated to study staff through the ESC website, and subjects were notified by telephone of their assignment groups"
Blinding : participant and personnel (performance bias)	High	"Due to the nature of the intervention, participant blinding was not possible"
Blinding : outcome assessment (detection bias)	High	The author's judgement of patient-reported outcome is « High » (see above) The author's judgement of observer-reported outcomes involving some judgement and of observer-reported outcomes not involving judgement is « Low » "the research assistant conducting assessments at the study conclusion (3 months) was blinded to group assignment"
Incomplete outcome data (attrition bias)	Low	"intention-to-treat" basis but results are provided only for completers 5 patients (4%) withdrew from the study and were evenly distributed among groups
Selective reporting (reporting bias)	High	Every outcome specified in the method section are reported in the results section but only the primary outcome is specified in the NCT registration
Other	Low	No competing interests related with the study and comparable baseline characteristics "Subjects in the pedometer plus website group had higher rates of inhaled long-acting muscarinic antagonist use compared to the pedometer alone group, p=0.01. There were no other differences in baseline characteristics by randomization group" "Conflicts of Interest Statement: Dr. Moy received an honorarium for consulting from Astra Zeneca. All other authors declare no relevant conflicts of interest"

Risk of bias in « the blinding » domain may differ between outcomes within a study, even if the same people were aware of intervention assignments during the trial. Therefore, the risk of bias was assessed independently for patient-reported outcomes, observer-reported outcome involving some judgement and observer-reported outcome not involving judgement in the « support for judgement » section. Using a conservative approach, the highest risk of bias for any outcomes measured within a given study was reported as the main author's judgement risk of bias.

HAD: anxiety and depression scale, **mMRC:** modified Mediral Research Council dyspnea score, **SF-36:** Short Form Health Survey, **QALY:** quality-adjusted life years, **AECOPD:** acute exacerbation of chronic obstructive pulmonary disease.

Appendix 4. Summary of findings – Pulmonary rehabilitation delivered using advanced telehealth technology compared with no pulmonary rehabilitation.

Pulmonary rehabiltiation delivered using advanced telehealth technology compared with no pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation using advanced telehealth technology compared with no pulmonary rehabiltiation

Intervention: pulmonary rehabilitation deivered using advanced telehealth technology

Comparison: no pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Exercise capacity (1-4 months) assessed with: 6MWT (meters)		MD **14.72 higher** (5.12 higher to 24.33 higher)	-	458 (4 RCTs)	⨁⨁◯◯ LOW [a]	Advanced telehealth technology to deliver pulmonary rehabilitation may result in a benefit on the 6MWT although that benefit is too small to be worthwhile according to the established minimum clinically important difference for this outcome (+25m)) [1]
Quality of life (1-4 months)	-	SMD **0.22 higher** (0 to 0.43 higher)	-	361 (4 RCTs)	⨁⨁◯◯ LOW [a]	Advanced telehealth technology to deliver pulmonary rehabilitation may result in an increase in quality of life although the uncertainty around this estimate ranged from no benefit to a moderate benefit. Converted back to an original unit, the estimate would be worthwhile (MD -4 out of 100 for the Saint George's Respiratory Questionnaire with lower value indicating a better quality of life) although the uncertainty around this estimate ranged from a clinically trivial benefit to a worthwhile benefit (95% CI -7 to 0) according to the established minimum clinically important difference for this outcome (-4%) [2,3]
Functional dyspnea (1-4 months) assessed with: Chronic Respiratory Questionnaire dyspnea sub-scale Scale from: 5 to 35		MD **1.8 higher** (0.75 lower to 4.35 higher)	-	84 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Higher value indicates lower dyspnea. The evidence is very uncertain about the effect of advanced telehealth technology to deliver pulmonary rehabilitation on functional dyspnea.
Functional dyspnea (1-4 months) assessed with: Modified Medical Research Council dyspnea score Scale from: 0 to 4		MD **0.1 lower** (0.69 lower to 0.49 higher)	-	29 (1 RCT)	⨁◯◯◯ VERY LOW [a,b]	Lower value indicates lower dyspnea. The evidence is very uncertain about the effect of advanced telehealth technology to deliver pulmonary rehabilitation on functional.

Appendix 4. Summary of findings – Pulmonary rehabilitation delivered using advanced telehealth technology compared with no pulmonary rehabilitation.

Pulmonary rehabiltiation delivered using advanced telehealth technology compared with no pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation using advanced telehealth technology compared with no pulmonary rehabiltiation

Intervention: pulmonary rehabilitation deivered using advanced telehealth technology

Comparison: no pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Health status (1-4 months) assessed with: COPD Assessment Test Scale from: 0 to 40		MD **0.82 lower** (2.06 lower to 0.43 higher)	-	354 (2 RCTs)	⨁⨁◯◯ LOW [a]	Lower value indicates better health status. Advanced telehealth technology to deliver pulmonary rehabilitation may not improve health status to any worthwhile extent according to the established minimum clinical important difference for this outcome (2.5 lower) [2,4]
Objective physical activity - steps/day (1-4 months)		MD **945.66 higher** (425.13 higher to 1466.2 higher)	-	546 (4 RCTs)	⨁⨁⨁◯ MODERATE [c]	Advanced telehealth technology to deliver pulmonary rehabilitation may results in a worthwhile increase in objective physical activity - steps/day although the uncertainty around this estimate ranged from a clinically trivial benefit to a very worthwhile benefit according to the established minimum clinical important difference for this outcome (+600-1100 steps per day) [5]
Acute exacerbation of COPD (9-12 months)	179 per 1 000	**227 per 1 000** (132 to 391)	**RR 1.27** (0.74 to 2.19)	238 (1 RCT)	⨁⨁◯◯ LOW [c,d]	The evidence is uncertain about the effect of advanced telehealth technology to deliver pulmonary rehabilitation on acute exacerbation of COPD.
Hospitalisation (9-12 months)	219 per 1 000	**291 per 1 000** (186 to 453)	**RR 1.33** (0.85 to 2.07)	262 (2 RCTs)	⨁⨁⨁◯ MODERATE [c]	The evidence is uncertain about the effect of advanced telehealth technology to deliver pulmonary on hospitalization (9-12 months).
Adverse event (1-4 months) assessed with: musculo-skeletal events	23 per 1 000	**131 per 1 000** (57 to 300)	**RR 5.66** (2.48 to 12.94)	582 (3 RCTs)	⨁⨁◯◯ LOW [a,e,f]	Advanced telehealth technology to deliver pulmonary rehabilitation may result in a substantial increase in the risk of musculo-skeletal adverse event.

Appendix 4. Summary of findings – Pulmonary rehabilitation delivered using advanced telehealth technology compared with no pulmonary rehabilitation.

Pulmonary rehabiltiation delivered using advanced telehealth technology compared with no pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation using advanced telehealth technology compared with no pulmonary rehabiltiation

Intervention: pulmonary rehabilitation deivered using advanced telehealth technology

Comparison: no pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Adverse event (9-12 months) assessed with: musculo-skeletal events	95 per 1 000	**279 per 1 000** (138 to 566)	**RR 2.93** (1.45 to 5.94)	238 (1 RCT)	⨁◯◯◯ VERY LOW a,d,e,g	Advanced telehealth technology to deliver pulmonary rehabilitation may result in a substantial increase in the risk of musculo-skeletal adverse event.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The quality of evidence was downgraded by two level due to the risk of bias of the included studies

b. The quality of evidence was downgraded because of the small number of studies available for this outcome and the impossibility to pool them within a meta-analysis

c. The quality of evidence was downgraded by one level due to the risk of bias of the included studies

d. Only one study available for this outcome

e. Adverse event are more likely to be reported in the intervention group when subjects are not blinded to the intervention

f. Very large effect

g. Large effect

ATT: advanced telehealth technology; **PR:** pulmonary rehabilitation; **SGRQ:** Saint George's Respiratory Questionnaire.

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Appendix 5. Summary of findings – Advanced telehealth technology to deliver pulmonary rehabilitation compared with in/outpatient pulmonary rehabilitation.

Pulmonary rehabilitation delivered using advanced telehealth technology compared with in/outpatient pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation delivered using advanced telehealth technology compared with centre-based pulmonary rehabilitation

Intervention: pulmonary rehabilitation delivered using advanced telehealth technology

Comparison: in/outpatient pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with in/outpatient pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Exercise capacity (1-4 months) assessed with: 6MWT (meters)		MD **5.56 higher** (25.60 lower to 36.72 higher)	-	224 (2 RCTs)	⨁⨁◯◯ LOW [a]	Advanced telehealth technology to deliver pulmonary rehabilitation may be similar to in/outpatient pulmonary on the 6MWT but this estimate came with very high uncertainty ranging from a harmful effect to a clinically worthwhile effect according to the established minimum clinically important difference for this outcome (+ 25m) [1]
Quality of life (1-4 months) assessed with: Saint George's Respiratory Questionnaire Scale from: 0 to 100		SMD **0.23 higher** (0.04 lower to 0.50 higher)	-	224 (2 RCTs)	⨁⨁◯◯ LOW [a]	Advanced telehealth technology to deliver pulmonary rehabilitation may be similar to or better than in/outpatient pulmonary rehabilitation in improving quality of life. Converted back to an original unit, the estimate would be worthwhile (MD -4 out of 100 for the Saint George's Respiratory Questionnaire, lower value indicating a better quality of life) although the uncertainty around this estimate ranged from a clinically trivial benefit to a very worthwhile benefit (95% CI -9 to 0) according to the established minimum clinically important difference for this outcome (-4%) [2,3]
Functional dyspnea	-	SMD **0.05 lower** (0.39 lower to 0.29 higher)	-	152 (2 RCTs)	⨁⨁◯◯ LOW [a]	Advanced telehealth technology to deliver pulmonary rehabilitation may be similar to in/out pulmonary rehabilitation on functional dyspnea. Converted back to an original unit, the estimates would be MD 0 out of 4 lower for the mMRC dyspnea scale (lower value indicates lower dyspnea) and the estimate revealed that the relative effect was unlikely to be clinically worthwhile (95% CI 0 to 0) according to the estabilised minimum important difference for this outcome (+1) [4,5]

Appendix 5. Summary of findings – Advanced telehealth technology to deliver pulmonary rehabilitation compared with in/outpatient pulmonary rehabilitation.

Pulmonary rehabilitation delivered using advanced telehealth technology compared with in/outpatient pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation delivered using advanced telehealth technology compared with centre-based pulmonary rehabilitation

Intervention: pulmonary rehabilitation delivered using advanced telehealth technology

Comparison: in/outpatient pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with in/outpatient pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Health status (1-4 months) assessed with: COPD Assessment Test Scale from: 0 to 40		MD **1.33 lower** (2.6 lower to 0.1 lower)	-	224 (2 RCTs)	⨁⨁◯◯ VERY LOW [a]	Lower score indicates better health status. Advanced telehealth technology to deliver pulmonary rehabilitation might be similar to or better than in/outpatient pulmonary rehabilitation on improving health status according to the established minimum clinically important difference for this outcome (+2.5) [6,7]
Objective physical activity - steps/day (1-4 months)	-	MD **436 higher** (138 lower to 1010 higher)	-	134 (1 RCT)	⨁⨁◯◯ LOW [a,b]	Advanced telehealth technology to deliver pulmonary rehabilitation may be similar to or better than in/outpatient patient pulmonary rehabilitation on improving improving objective physical activity - steps/day according to the established minimum clinically important difference for this outcome (+600-1100 steps/day) [8]
Acute exacerbation of COPD (9-12 months) - not reported	-	-	-	-	-	Outcome not reported
Hospitalisation (9-12 months) - not reported	-	-	-	-	-	Outcome not reported
Adverse event (1-4 months)	54 per 1 000	**13 per 1 000** (3 to 61)	**RR 0.24** (0.05 to 1.13)	224 (2 RCTs)	⨁⨁◯◯ LOW [a,c]	The evidence is uncertain about the relative effect of advanced telehealth technology to deliver pulmonary rehabilitation on adverse event (1-4 months).
Adverse event (9-12 months) - not reported	-	-	-	-	-	Outcome not reported

Appendix 5. Summary of findings – Advanced telehealth technology to deliver pulmonary rehabilitation compared with in/outpatient pulmonary rehabilitation.

Pulmonary rehabilitation delivered using advanced telehealth technology compared with in/outpatient pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation delivered using advanced telehealth technology compared with centre-based pulmonary rehabilitation

Intervention: pulmonary rehabilitation delivered using advanced telehealth technology

Comparison: in/outpatient pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with in/outpatient pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The quality of evidence was downgraded by two level due to the risk of bias of the included studies

b. Only one study assessed this outcome

c. Adverse event are more likely to be reported in the intervention group when subjects are not blinded to the intervention

ATT: advanced telehealth technology; **PR:** pulmonary rehabilitation; **mMRC:** modified Medical Research Council dyspnea score.

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Appendix 6. Summary of findings – Pulmonary rehabilitation delivered using advanced telehealth technology compared with home-based pulmonary rehabilitation.

Pulmonary rehabilitation delivered using advanced telehealth technology compared with home-based pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation using advanced telehealth technology compared with home-based pulmonary rehabilitation not using advanced telehealth technology

Intervention: Pulmonary rehabilitation delivered using advanced telehealth technology

Comparison: home-based pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with home-based pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Exercise capacity (1-4 months) assessed with: 6MWT (meters)		MD **1.75 higher** (15.49 lower to 18.99 higher)	-	231 (3 RCTs)	⨁⨁◯◯ LOW [a]	Advanced telehealth technology to deliver pulmonary rehabilitation may be similar to home-based pulmonary rehabilitation according to the minimum clinically important difference for this outcome (+25m) [1]
Quality of life (1-4 months)	-	SMD **0.79 higher** (0.04 lower to 1.62 higher)	-	171 (3 RCTs)	⨁◯◯◯ VERY LOW [a,b]	Advanced telehealth technology to deliver pulmonary rehabiltiation may further improve quality of life compared with home-based pulmonary rehabilitation but this estimate came with uncertainty ranging from no benefit to a very worthwhile benefit. Converted back to an original unit, the estimate would be very worthwhile (MD -14 out of 100, lower value indicating a better quality of life) but this estimate also came with uncertainty ranging from a similar effect to a very worthwhile benefit (95% CI 28 lower to 1 higher) according to the minimum clinically important difference for this outcome (-4%) [2,3]
Functional dyspnea (1-4 months) assessed with: Chronic Respiratory Questionnaire dyspnea sub-scale Scale from: 5 to 35		MD **1.97 higher** (0.03 lower to 3.97 higher)	-	123 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b]	Higher value indicates lower dyspnea. Advanced telehealth technology to deliver pulmonary rehabiltiation might provide a very worthwhile effect compared with home-based pulmonary rehabilitation although the estimate came with uncertainty ranging from a similar effect to a very worthwhile effect according to the estabilisehd miminum clinically important difference for this outcome (+0.5) [2]

Appendix 6. Summary of findings – Pulmonary rehabilitation delivered using advanced telehealth technology compared with home-based pulmonary rehabilitation.

Pulmonary rehabilitation delivered using advanced telehealth technology compared with home-based pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation using advanced telehealth technology compared with home-based pulmonary rehabilitation not using advanced telehealth technology

Intervention: Pulmonary rehabilitation delivered using advanced telehealth technology

Comparison: home-based pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with home-based pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Health status (1-4 months) assessed with: COPD Assessment Test Scale from: 0 to 40		MD **0.4 lower** (2.5 lower to 1.7 higher)	-	88 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	Lower score indicates better health status. Advanced telehealth technology to deliver pulmonary rehabilitation might be similar to or better than home-based PR in improving in health status according to the established minimum clinically important difference for this outcome (+2.5) [3]
Objective physical activity - steps/day (1-4 months)		MD **804 higher** (105.27 higher to 1502.73 higher)	-	109 (1 RCT)	⨁⨁◯◯ LOW [c,d]	The relative effect of advanced telehealth technology to deliver pulmonary rehabilitation may be worthwhile compared with home-based pulmonary rehabilitation in improving objective physical activity - steps/day although this estimate came with uncertainty ranging from a clinically trivial benefit to a very worthwhile benefit according to the established minimum clinically important difference for this outcome (+600-1100 steps/day) [4]
Acute exacerbation of COPD (9-12 months)	417 per 1 000	**83 per 1 000** (21 to 342)	**RR 0.20** (0.05 to 0.82)	48 (1 RCT)	⨁◯◯◯ VERY LOW [c,d,e]	The evidence is very uncertain about the effect of advanced telehealth technology to deliver pulmonary rehabilitation on acute exacerbation of COPD but it may provide a worthwhile relative effect
Hospitalisation (9-12 months)	556 per 1 000	**294 per 1 000** (106 to 822)	**RR 0.53** (0.19 to 1.48)	153 (2 RCTs)	⨁⨁⨁◯ MODERATE [d]	The evidence is uncertain about the effect of advanced telehealth technology to deliver pulmonary rehabilitation on hospitalization.

Appendix 6. Summary of findings – Pulmonary rehabilitation delivered using advanced telehealth technology compared with home-based pulmonary rehabilitation.

Pulmonary rehabilitation delivered using advanced telehealth technology compared with home-based pulmonary rehabilitation for chronic obstructive pulmonary disease

Patient or population: chronic obstructive pulmonary disease

Setting: Home-based pulmonary rehabilitation using advanced telehealth technology compared with home-based pulmonary rehabilitation not using advanced telehealth technology

Intervention: Pulmonary rehabilitation delivered using advanced telehealth technology

Comparison: home-based pulmonary rehabilitation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with home-based pulmonary rehabilitation	**Risk with advanced telehealth technology to deliver pulmonary rehabilitation**				
Adverse event (1-4 months)	185 per 1 000	**233 per 1 000** (113 to 481)	**RR 1.26** (0.61 to 2.60)	114 (1 RCT)	⨁◯◯◯ VERY LOW [c,d,f]	The evidence is very uncertain about the effect of advanced telehealth technology to deliver pulmonary rehabilitation on adverse event.
Adverse event (9-12 months) - not reported	-	-	-	-	-	Oucome not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD:** Mean difference; **SMD:** Standardised mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

a. The quality of evidence was downgraded by two level due to the risk of bias of the included studies

b. One study could not have been pooled within the meta-analysis

c. Only one study assessed this outcome

d. The quality of evidence was downgraded by one level due to the risk of bias of the included studies

e. Very small sample size

f. Adverse event are more likely to be reported in the intervention group when subjects are not blinded to the intervention

ATT: advanced telehealth technology; **PR:** pulmonary rehabilitation; **SGRQ:** Saint George's Respiratory Questionnaire.

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4. Demeyer H, Burtin C,Hornikx M,Camillo CA,Van Remoortel H,Langer D,et al.. The Minimal Important Difference in Physical Activity in Patients with COPD.. PLoS One; 2016.

Box 1. Primary outcomes.

- Exercise capacity measured either by field tests, endurance exercise testing (constant workload exercise testing or endurance shuttle walk test) or incremental cardiopulmonary exercise testing
- Quality of life (assessed either with a general or a disease-specific questionnaire)
- Functional dyspnea
- Cost-effectiveness analysis of the intervention

Box 2. Secondary outcomes.

- Health status using the COPD Assessment Test (CAT) or other validated health status questionnaire
- Peripheral muscle strength measured either by the maximal voluntary contraction (MVC), the one repetition maximum (1RM), or peak torque through isokinetic measurement
- Physical activity:
    a. objectively assessed either by the step number, the metabolic equivalent of task (MET)-hour, the time spent at less than 3METs or any objective measurement performed with an activity monitor and reported as "activity" raw unit according the device used
    b. subjectively assessed using any self-reported questionnaire
- Respiratory function: forced expired volume in 1s (FEV_1) and forced vital capacity (FVC)
- Anxiety and depression using questionnaires
- Self-efficacy using questionnaires
- Acute exacerbations[a]
- Hospitalisation[a]
- Mortality[a]
- Adherence and completion
- Adverse outcome

[a] Only long-term data were considered.

III.3. Outils existants et nouveaux outils pour optimiser les effets du réentrainement à l'exercice et le maintien des acquis

Les données issues des contributions originales proposées au cours de cette thèse confirment l'idée que la place des adjuvants à la réhabilitation respiratoire est loin d'être clairement établie (207, 208). En effet, certains adjuvants comme la VNI, sont associés à des résultats contradictoires dans la littérature. La complexité des réglages peut contribuer à expliquer ces résultats. Par conséquent, d'autres approches, aux réglages plus simples, méritent d'être évaluées.

Le haut débit nasal est une nouvelle modalité de traitement, nécessitant peu de réglages. Elle permet de délivrer un mélange gazeux à haut débit (jusqu'à 60 L/min) grâce à un dispositif électrique. Pour éviter tout évènement indésirable lié à la délivrance d'un tel débit, celui-ci est humidifié et réchauffé (jusqu'à 37°C). Le haut débit nasal a largement été étudié dans les services de réanimation pédiatriques et adultes. Dans ce contexte, elle semble plus efficace que l'oxygénothérapie conventionnelle et aussi efficace que la ventilation non invasive pour prévenir la mortalité en situation de décompensation respiratoire hypoxémique aiguë (209-213) et serait mieux tolérée (214). Elle pourrait également permettre le contrôle de l'hypercapnie chez les patients atteints de BPCO (215).

Il est possible de régler trois paramètres sur un dispositif de thérapie à haut débit humidifié : le débit, la température et l'humidité du mélange gazeux délivré. Ces trois paramètres ont des effets physiologiques différents contribuant à expliquer le bénéfice du haut débit nasal :

Effets liés au haut débit : Le haut débit produit par le haut débit nasal permet la génération d'une pression positive expiratoire (216). Celle-ci dépend de l'ouverture ou la fermeture de la bouche et est positivement liée au débit utilisé (216). Par ailleurs, le haut débit nasal permet un rinçage du gaz carbonique présent dans les voies aériennes supérieures, réduisant ainsi l'espace mort physiologique (217). A nouveau, cet effet semble positivement lié au débit et à la présence de fuites (217). Enfin, cet outil peut être couplé à une oxygénothérapie. Dans ce contexte, l'utilisation d'un haut débit offre l'avantage de couvrir entièrement le débit inspiratoire du patient, prévenant toute dilution de l'oxygène avec l'air ambiant et permettant ainsi le maintien d'une fraction inspirée en oxygène stable (218).

Effets liés au réchauffement et à l'humidification du mélange gazeux inspiré : Les recherches menées dans le modèle animal ont révélé que l'humidité et la température étaient des facteurs-clés pour la fréquence de battement des cils trachéaux et le transport du mucus. Les résultats optimaux étaient obtenus pour une température de 37°C et une humidité de 100% (219).

Cependant, malgré ces données prometteuses sur les effets du haut débit nasal, il en existe peu concernant ses effets chez les patients atteints de BPCO à l'état stable. Par ailleurs, de récentes données issues de notre laboratoire suggèrent qu'elle ne serait pas efficace pour améliorer la performance à l'effort de patients atteints de BPCO récupérant d'une exacerbation (220). Néanmoins, ses effets à l'effort chez les patients stables ont été peu explorés. Aussi, l'objectif de la revue systématique présentée ci-dessous est d'évaluer les effets de ce traitement chez les patients atteints de BPCO à l'état stable.

Étude n°10

Effets du haut débit nasal au repos et à l'effort chez les patients atteints de BPCO, à l'état stable – Revue systématique et méta-analyse

Nasal High Flow for Stable Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

T. Bonnevie, M. Elkins, C. Paumier, C. Médrinal, Y. Combret, M. Patout, JF. Muir, A. Cuvelier, FE. Gravier, G. Prieur

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Nasal High Flow for Stable Patients with Chronic Obstructive Pulmonary Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

There is a growing body of evidence supporting the use of nasal high flow (NHF) to treat acute respiratory failure, particularly in Chronic Obstructive Pulmonary Disease (COPD) patients. Conversely, there are sparse data evaluating its effects in stable COPD patients.

We identified randomized controlled trial comparing the effects of delivering air or oxygen *via* NHF, compared with delivering the same gas without NHF, in stable COPD patients through a systematic search using MEDLINE, CENTRAL, Science Direct, and others sources until January 2019. Study selection, data extraction and assessment of the risk of bias (using the Cochrane Risk of Bias tool) was performed by two independent authors.

We included 6 studies (339 participants). Our meta-analysis showed a significant reduction of arterial carbon dioxide pressure ($PaCO_2$) at long (two studies, MD −3 mmHg, [95% Confidence interval (CI) −4 to −2]) and short-term (two studies, MD -3 mmHg [95% CI −4 to −2]). NHF significantly improved quality of life on the St George's Respiratory Questionnaire (two studies, MD −5 out of 100, [95% CI −8 to −2]). NHF significantly reduced the rate of acute exacerbation at 1 year (one study, rate ratio: 0.6, [95% CI 0.6 to 0.7]). NHF did not significantly improve exercise capacity, hospitalization rate or mortality, but improved breathing pattern.

NHF reduced $PaCO_2$, acute exacerbation and improved quality of life in stable COPD patients. Further long-term studies are needed to confirm the present results and provide more data on patient-centered outcome such as quality of life, exacerbation, hospitalization and mortality.

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KEYWORDS
Pulmonary disease, chronic obstructive; nasal high-flow; high-flow cannula; meta-analysis

List of abbreviations

COPD	chronic obstructive pulmonary disease;
HR	heart rate
FEV1	forced expiratory volume in 1s;
FVC	forced vital capacity;
NHF	nasal high-flow;
NIV	noninvasive ventilation;
mMRC	modified Medical Research Council dyspnea scale;
MV	minute ventilation;
$PaCO_2$	arterial carbon dioxide partial pressure;
Pga	gastric pressure;
Poes	esophageal pressure;
$PtcCO_2$	transcutaneous arterial carbon dioxide partial pressure;
Ptdia	transdiaphragmatic pressure;
REM	rapid eye movement;
RR	respiratory rate;
RSBI	rapid shallow breathing index;
SpO2	pulsed oxygen saturation;
StO_2	transcutaneous oxygen saturation;
SaO_2	arterial oxygen saturation;
TcO_2	transcutaneous oxygen;
Vt	tidal volume.

Introduction

COPD is a worldwide cause of morbi-mortality with a growing burden [1, 2]. This disease progressively leads to chronic respiratory insufficiency which can lead to hypoxia and hypercapnia [3], each of which is associated with poor outcomes [3, 4].

Long-term oxygen therapy reduces both hypoxia and mortality significantly in severely hypoxic patient with COPD [5] whereas intermittent noninvasive ventilation (NIV) with high pressure has been used to reduce arterial

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Supplemental data for this article can be accessed at https://doi.org/10.1080/15412555.2019.1672637.

carbon dioxide and improve mortality in chronic hypercapnic COPD patients (>55 mmHg) [6, 7].

Unfortunately, there are important drawbacks associated with the use of NIV, including interface discomfort, excessive high air pressure, sleep disturbance and intolerability due to patient-ventilator asynchrony, each of which can lead to poor compliance or treatment failure [8–11]. Therefore, alternative strategies are warranted.

Nasal high flow (NHF) delivers heated and humidified high flow air (up to 60 L/min) through nasal canula, providing promising physiological benefits such as positive airway pressure [12] or upper airway CO_2 washout [13]. It can be used in association with oxygen and offers in this situation the advantage to match the patient's inspiratory flow, preventing any dilution of the inspired fraction of oxygen [14]. NHF has widely been studied in adult intensive care units and seems better than conventional oxygen therapy and as effective as NIV with regards to mortality to treat hypoxemic acute respiratory failure [15–19]. Moreover, it may be more comfortable than conventional treatments [20] and could help to control hypercapnia in patients with COPD [21].

Despite this promising background evidence about NHF, there are sparse data evaluating its effects on clinically important outcome in stable patients with COPD.

Therefore, the overall aim of this review was to summarize the available evidence assessing the effects of delivering air or oxygen *via* NHF, compared with delivering the same gas without NHF, in people with stable COPD.

Method

Study registration and methodology

The protocol of this systematic review and meta-analysis was prospectively registered at PROSPERO (www.crd.york.ac.uk/prospero; CRD: 42018103358). It has been designed according to the *Cochrane Handbook for Systematic Reviews of Interventions* [22] and reported according to the PRISMA statement.

Criteria for considering studies for this review

Types of studies

Parallel and cross-over randomized trials, included those in the format of an abstract, assessing one or more of the considered outcomes.

Type of participants

Adult patients with stable COPD (no acute exacerbation in the previous 3 weeks), of any age, diagnosed based on the individual study's criteria. Studies with a mixed population of COPD and other respiratory disease(s) could be included if the data for the participants with COPD could be extracted separately.

Type of intervention

NHF with air, or supplemental oxygen if indicated by the patient's clinical status, compared with the same gas delivered without NHF.

Type of outcome measures

Primary outcomes.

1. Arterial carbon dioxide partial pressure measured transcutaneously ($PtcCO_2$) or by arterial blood gases ($PaCO_2$);
2. Arterial oxygen partial pressure measured transcutaneously (TcO_2) or by arterial blood gases (PaO_2);
3. pH measured by arterial blood gases;
4. Quality of life (assessed either with a general or a disease-specific questionnaire);
5. Deaths;
6. Number of acute exacerbations per year;
7. Number of hospitalizations per year;

Secondary outcomes.

1. Oxygen saturation measured by pulse or transcutaneous oximetry (SpO_2 and StO_2 respectively) or by arterial blood gases (SaO_2);
2. Cardiorespiratory function (heart rate (HR); forced expired volume in 1s (FEV_1); forced vital capacity (FVC);
3. Breathing pattern (volume tidal (Vt); respiratory rate (RR); minute ventilation (MV); rapid shallow breathing index (RSBI));
4. Respiratory mechanics (gastric pressure (Pga); esophageal pressure (Poes); transdiaphragmatic pressure (Ptdia); end-expiratory lung impedance);
5. Dyspnea assessed either during or after an exercise or at rest;
6. Exercise capacity measured either by a maximal cardiopulmonary exercise testing or field tests;
7. Objective or self-reported physical activity;
8. Comfort and patient preference;
9. Adverse events.

Search methods for identification of studies

Electronic searches

MEDLINE, CENTRAL, Science Direct, Scopus, PEDro, OpenGrey and Greylit were searched from inception up to January 2019 for relevant studies in English or French. Reference list of the included studies were also checked for eligible studies.

Detailed searching strategy is shown in eAppendix 1.

Data collection and analysis: see eAppendix 1.

Study selection, data extraction and assessment of the risk of bias (using the Cochrane Risk of Bias tool[22]) was performed by two independent authors. Any disagreement was resolved by discussion or the intervention of a third author.

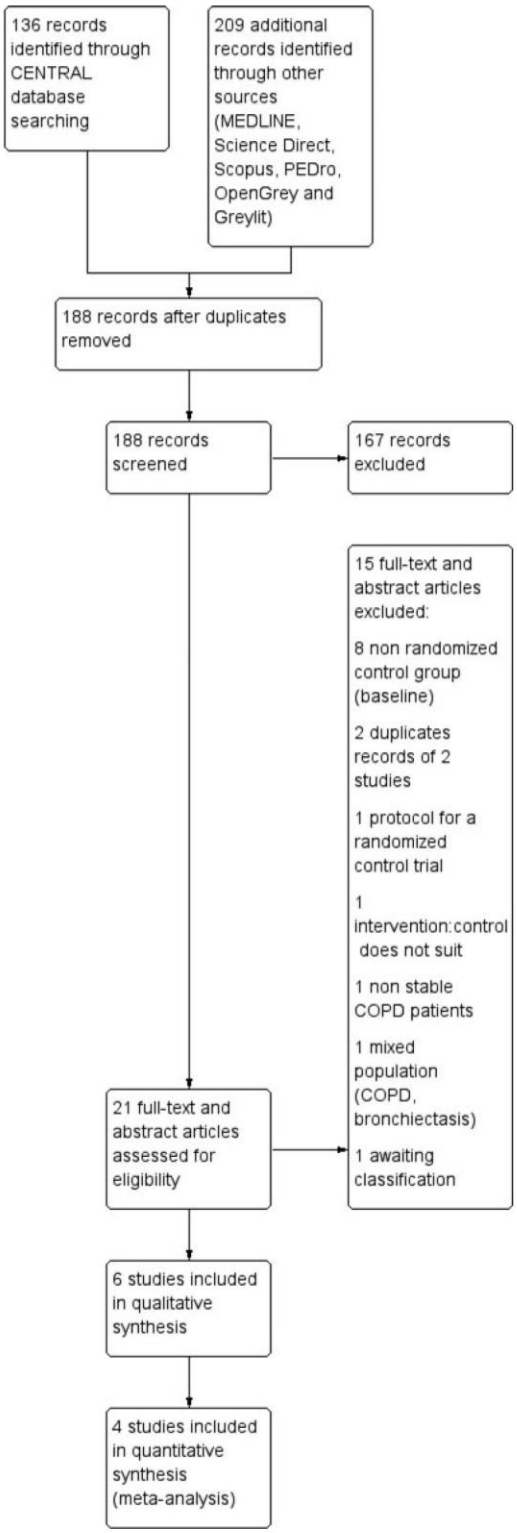

Figure 1. Study flow diagram.

Data synthesis

Heterogeneity was assessed using the I^2 and Chi^2 statistic, considering values $I^2 \geq 50\%$ as a sign of moderate to high heterogeneity. Meta-analysis was performed with a fixed or a random-effect model according to heterogeneity. RevMan 5.3.5 was used for analysis. The quality of evidence was rated using the GRADE system.

Results

Descriptions of studies and participants

188 records were retrieved from database searching after removal of duplicates and 6 studies [23–28] were included giving a total of 339 participants. See Figure 1.

There was a good agreement between authors for the study selection (kappa score: 0.71).

Characteristics (methods, participants, intervention and outcomes) of the included studies are shown in Table 1.

Five studies were reported as full-text publications [23–25, 27, 28] while one was available as an abstract only [26]. Three assessed the short-term effects of NHF [24–26], two assessed the long-term effects [27, 28] and the remaining study assessed NHF during exercise [23].

Patients with chronic hypoxemia [24, 28], or both chronic hypoxemia and hypercapnia [26, 27] were specifically included in four studies. When patients had oxygen during the control intervention, the oxygen flow during NHF was adjusted as necessary to maintain the same baseline transcutaneous oxygen saturation (SpO_2) [23, 24, 27, 28].

Risk of bias in included studies

The risk of bias among the included studies is depicted in Figure 2A and Figure 2B. The detailed evaluation is available in eAppendix 2.

Effects of interventions

The results for the three categories of trials (long-term, short-term, and during exercise) are detailed below. The overall findings are also summarized in Table 2.

Long-term effects

Two studies including 229 participants contributed data on the long-term effects of NHF [27, 28]. The follow-up period for these studies ranged from 6 weeks to 12 months.

Primary outcomes

Arterial carbon dioxide pressure. Meta-analysis of two studies showed a statistically significant benefit for NHF on $PaCO_2$ (pooled MD −3 mmHg, 95% CI −4 to −2; I^2=0%; Figure 3A).

Nagata et al. also assessed single night PtcCO2 (without NHF) [27]. They found a significant improvement in the mean median $PtcCO_2$ (MD −5mmHg, 95% CI −8 to −2) in favor of NHF.

Arterial oxygen pressure. One study was available for this outcome (total 29 participants) [27]. There was no difference between NHF and control in PaO_2 (MD −3 mmHg, 95% CI −9 to 3).

Table 1. Characteristics of included studies.

First author (date)	Methods	Participants	Intervention	Outcomes	Notes
Long-term					
Nagata (2017)	Randomized cross-over study	29 patients with stable hypoxic and hypercapnic COPD	NHF group: AIRVO 20 to 40 L/min with O_2 adjusted to maintain SpO_2>88% 7h/day	Primary: QOL	No washout period
	Data collection at 6 weeks for each intervention	(mean age 75 years, 90% males, mean FEV_1 29% predicted)	LTOT group: O_2 1 to 2 L/min or usual care	Secondary: PCO_2, nocturnal $TcCO_2$, PaO_2, pH, SaO_2, FEV_1, FVC, dyspnea, physical activity, exercise capacity, adverse events and acute exacerbation	
Storgaard (2018)	Randomized parallel study	200 COPD patients with chronic hypoxemic respiratory failure	NHF group: AIRVO 20 L/min with O_2 adjusted to maintain SpO_2>88% 6-7h/day (>8h recommended)	Primary: acute exacerbation	
	Data collection every 3 months during 12 months	(mean age 71 years, 40% males, mean FEV_1 31% predicted)	LTOT group: conventional oxygen nasal cannula 1- to 2 L/min	Secondary: PCO_2, FEV_1, dyspnea, exercise capacity, QOL, hospitalization and mortality	
Short-term					
Fraser (2016)	Randomized cross-over study	30 patients with stable hypoxic COPD	NHF group: AIRVO 30 L/min with O_2 to reach the same FiO_2 than with conventional oxygen	PCO_2, PO_2, SaO_2, Vt, RR, HR, MV, EELI, dyspnea and comfort	Only males Primary and secondary outcomes not differentiated
	2.5 to 3 hours data collection period	(mean age 74 years, 100% males, FEV_1% not reported)	LTOT group: conventional oxygen nasal cannula 2 to 4 L/min 20min (×2)		
Mckinstry (2018)	Randomized cross-over study	48 patients with stable COPD	NHF group: AIRVO 15 L/min, 30 L/min and 45 L/min of air	Primary: PCO_2	
	>2.5 hours data collection period	(mean age 69 years, 60% males, FEV_1 53% predicted)	Control group: Room air only, without NHF 20min (×2) 15min washout	Secondary: SaO_2, RR, HR	
Nilius (2013)	Randomized cross-over study	20 patients with stable hypoxic and hypercapnic COPD	NHF group: TNI20oxy, 20 L/min with O_2 (2 to 3 L/min)	Nocturnal $TcCO_2$, arterial blood gases and sleep indices	Primary and secondary outcomes not differentiated
	>6 hours data collection period	(mean age 66 years, % males not reported, FEV_1 28% predicted)	LTOT group: conventional oxygen nasal cannula 2 to 3 L/min		
During exercise					
Cirio (2016)	Randomized cross-over study	12 patients with stable COPD	NHF group: AIRVO 55 to 60L/min	Primary: exercise capacity	Venturi mask: -connected to compressed air in place of oxygen -additional oxygen to maintain SaO_2 >88%
	Data collection period: 3 separate days	Ventilatory limitation (MVV-peakVe < 11 L/min) Limited to effort (6MWT <75%) (mean age 70 years, 83% males, mean FEV_1 35% predicted)	Control group: Venturi mask (with or without O_2) Material: Cycle-ergometer (44 ± 17W) Process: Incremental test (day 1) In a random order, two constant-load exercise tests (day 2 and 3), at 75% of the maximal workload achieved during the incremental test (day 1) with HFNC or Venturi mask	Secondary: SaO_2, dyspnea and adverse events	

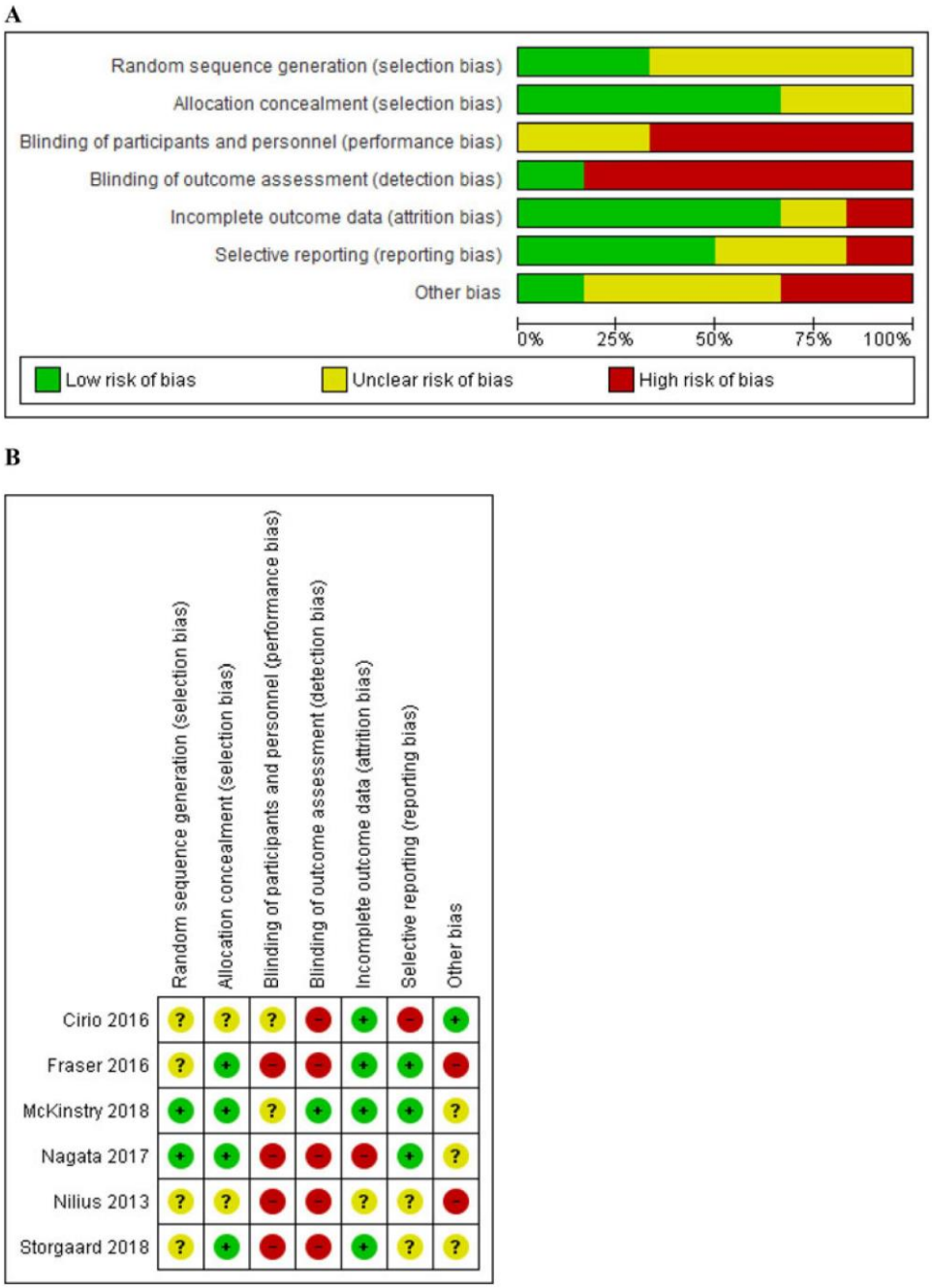

Figure 2. A/Risk of bias among the included studies. Review authors' judgements about each risk of bias item presented as percentages across all included studies; B/Risk of bias summary. Review authors' judgements about each risk of bias item for each included study.

pH. One cross-over study (total 29 participants) found a significant increase in pH in favor of NHF (MD 0.02, 95% CI 0 to 0.04) [27]. Conversely, Storgaard et al. (total 200 participants) found no significant difference in baseline-adjusted changes in pH (detailed data not available on the original report and we had no answer from the author). The quality of evidence was "very low".

Quality of life. The two studies that measured quality of life both used the Saint George's Respiratory Questionnaire, which is measured from 0 (no impairment) to 100 (maximum impairment). The result showed a statistically significant effect in favor of NHF (pooled MD −5, 95% CI −8 to −2; I^2=11%; Figure 4).

Mortality. One study was available for this outcome (total 200 participants) [28]. There was no difference between NHF and control in death events (risk ratio = 1.25, 95% CI 0.62 to 2.53).

Acute exacerbation. Because of the relatively short-term evaluation for this particular outcome in one study (6 weeks) and its cross-over design [27], meta-analysis was deemed inappropriate and results are reported narratively instead.

Table 2. Summary of findings.

Nasal high-flow compared to usual care for stable patients with chronic obstructive pulmonary disease

Patient or population: stable patients with chronic obstructive pulmonary disease
Setting:
Intervention: Nasal high-flow
Comparison: usual care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with usual care	Risk with Nasal high-flow				
Arterial carbon dioxode partial pressure (mmHg); follow up: 1.5-12 months		The mean arterial carbon dioxode partial pressure (mmHg) in the intervention group was 2,95 lower (4,27 lower to 1,64 lower)	–	229 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	Long-term nasal high-flow likely reduces arterial carbon dioxode partial pressure (mmHg) slightly.
Arterial carbon dioxide partial pressure (mmHg): acute effects with NHF		The mean arterial carbon dioxide partial pressure (mmHg): acute effects with NHF in the intervention group was 2,73 lower (3,8 lower to 1,65 lower)	–	78 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	Acute session of nasal high-flow likely reduces arterial carbon dioxide partial pressure (mmHg) slightly.
Quality of life assessed with: Saint George's Respiratory Questionnaire (%); Scale from: 0 to 100; follow up: 1.5-12 months		The mean quality of life in the intervention group was 5,29 lower (8,3 lower to 2,28 lower)	–	229 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	Lower value indicates a better quality of life. Long-term nasal high-flow likely results in a large improvement in quality of life, higher than the defined minimum important difference for this outcome (4 points).[1]
Mortality; follow up: 1 years	120 per 1 000	**150 per 1 000** (74 to 304)	**RR 1.25** (0.62 to 2.53)	200 (1 RCT)	⨁⨁◯◯ LOW[b]	The evidence suggests that long-term nasal high-flow does not improve mortality.
Rate of acute exacerbation of COPD; follow up: 100 patient years	50 per 1 000	**31 per 1 000** (27 to 36)	**Rate ratio 0.63** (0.55 to 0.72)	200 (1 RCT)	⨁⨁◯◯ LOW[b]	Long-term nasal high-flow may result in a reduction in rate of acute exacerbation of COPD.
Rate of hospitalization; follow up: 100 patient years	122 per 1 000	**109 per 1 000** (84 to 140)	**Rate ratio 0.89** (0.69 to 1.15)	200 (1 RCT)	⨁⨁◯◯ LOW[b]	The evidence suggests that nasal long-term high-flow does not reduce rate of hospitalization.
Dyspnea assessed with: mMRC dyspnea scale; Scale from: 0 to 4; follow up: 1-1.5 months		The mean dyspnea in the intervention group was 0,27 lower (0,41 lower to 0,13 lower)	–	229 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	Lower value indicates an improvement in dyspnea. Long-term nasal high-flow probably results in little to no difference in dyspnea.
Exercice capacity assessed with: six-minute walk test (m); follow up: 1.5-12 months		The mean exercice capacity in the intervention group was 18,19 higher (9,18 lower to 45,55 higher)	–	229 (2 RCTs)	⨁◯◯◯ VERY LOW[c,d,e]	The evidence is very uncertain about the effect of nasal high-flow on exercice capacity.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a]The quality of evidence was downgraded to moderate due to the risk of bias of the included studies
[b]The quality of evidence was downgraded to moderate due to the risk of bias of the included studies.
[c]The quality of evidence was downgraded due to the risk of biais of the included studies.
[d]Included studies showed divergent results and high heterogeneity.
[e]Wide confidence interval.

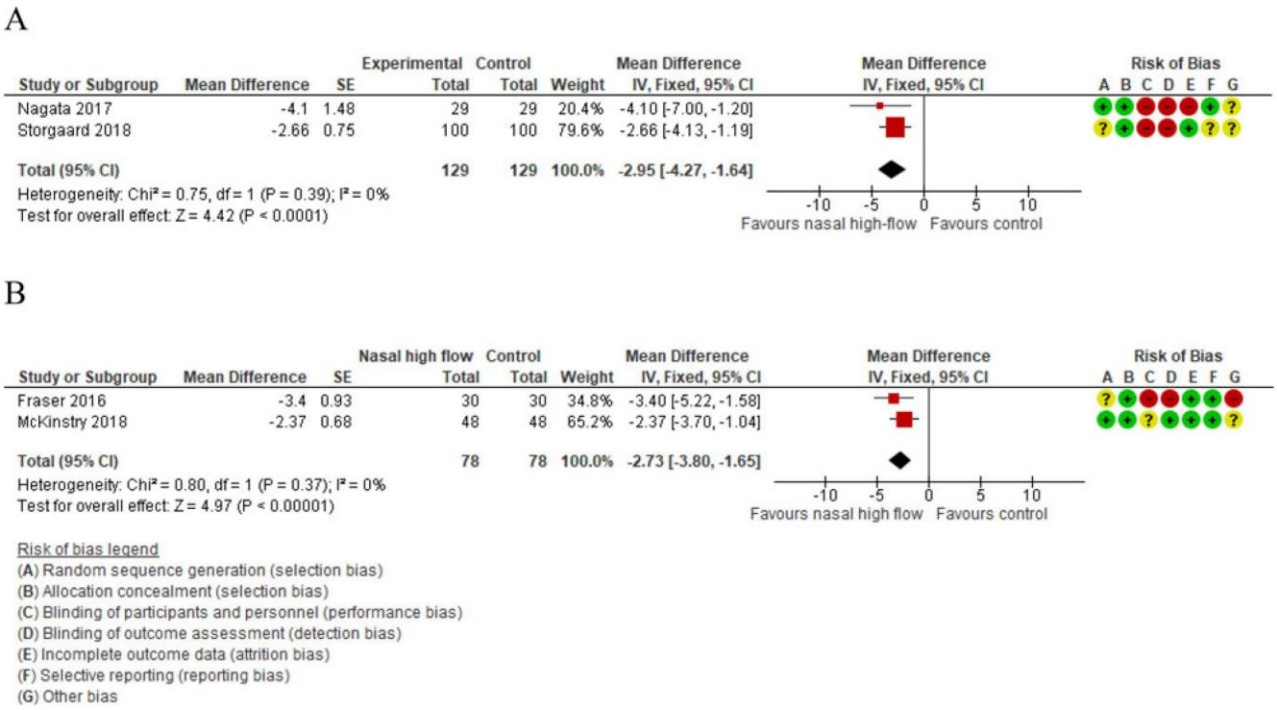

Figure 3. Long-term (A) and short-term (B) effects of nasal high-flow on arterial carbon dioxide pressure (mmHg).

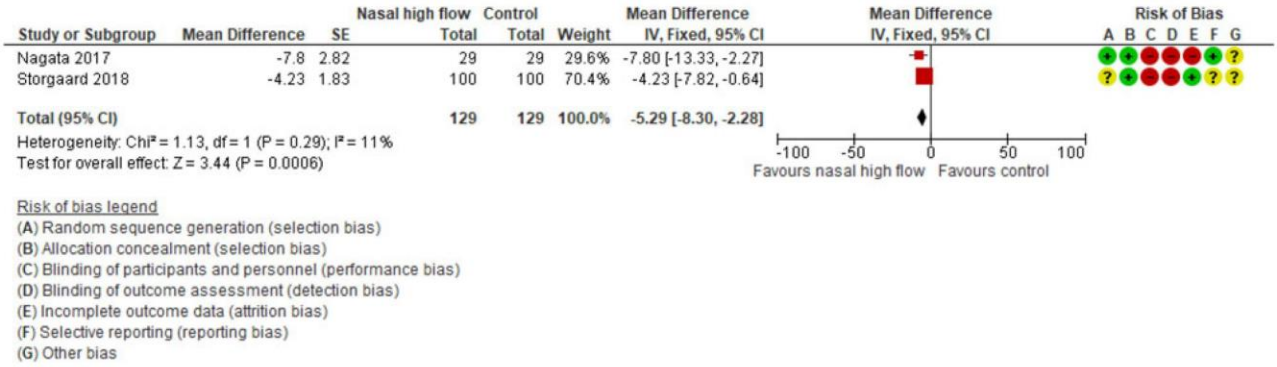

Figure 4. Long-term effects of nasal high-flow on quality of life (Saint George's Respiratory Questionnaire, %).

One cross-over study (total 29 participants) [27] reported three exacerbation's of COPD with long-term oxygen (10.3%) and none with NHF over a 6-week period of treatment. One parallel study (total 200 participants) reported a significant reduction in acute exacerbations of COPD (rate ratio: 0.63, 95% CI 0.55 to 0.72) at 1 year.

Hospitalization. One study was available for this outcome (total 200 participants) [28]. There was no difference between NHF and control in patient-year hospitalization rate (rate ratio: 0.89, 95% CI 0.69 to 1.15).

Secondary outcomes. Results for the secondary outcomes are shown in eAppendix 3. The quality of evidence ranged from "moderate" (significant improvement in the mMRC dyspnea scale with NHF) to "low" (no significant effects FEV_1(%)) and "very low" (no significant effects on SpO_2, exercise capacity, and physical activity).

Short-term effects

Three cross-over studies including 98 participants contributed data on the short-term effects of NHF [24–26].

Primary outcomes

Arterial carbon dioxide pressure

Two studies including 78 participants contributed data on arterial carbon dioxide pressure [24, 25]. Meta-analysis showed statistically significant effects of nasal high flow on arterial carbon dioxide pressure (pooled MD −3 mmHg, 95% CI −4 to −2; I^2=0%; Figure 3B).

One study including 20 participants assessed single-night nocturnal PtcCO2 [26]. Nilius et al. found a significant improvement both in the non-REM PtcCO2 (MD −1 mmHg, 95% CI −3 to −0) and in the REM PtcCO2 (MD −2 mmHg, 95% CI −3 to −1) with NHF.

Arterial oxygen pressure

One study was available for this outcome (total 30 patients) [24]. There was a significant difference between NHF and control in TcO_2 in defavor of the COPD patients randomized to the NHF group (MD −4 mmHg, 95% CI −7 to −1). The quality of evidence was "very low".

Secondary outcomes

Results for the secondary outcomes are shown in eAppendix 3. The quality of evidence ranged from "very low" (no significant effects on SpO_2, HR and MV, significant improvement in Vt and end-expiratory lung impedance and significant worsening in dyspnea and comfort with NHF) to "low" (significant improvement in RR with NHF).

During exercise

Only one cross-over study (12 participants) assessed the effects of during exercise NHF (constant workload exercise testing) compared with oxygen [23]. The overall quality of evidence was "very low" (significant improvement in endurance time, isotime dyspnea and isotime SaO_2).

Detailed results are shown in eAppendix 4.

Discussion

The main findings of this meta-analysis were that NHF significantly reduced $PaCO_2$ (about -3mmHg) compared with usual care. Moreover, it significantly increased health-related quality of life and breathing pattern, and reduced acute exacerbations of COPD. NHF had no significant effects on mortality, hospitalization rate, pulmonary function and exercise capacity. One short-term study revealed that NHF could reduce TcO_2 and worsen dyspnea and comfort. Finally, the use of NHF during exercise might improve endurance capacity and dyspnea.

The improvement in $PaCO_2$ was found both at short and long term. The main explanation for the short-term improvement lies in the improvement of the breathing pattern which is supported by our results suggesting an increase in Vt and a decrease RR. Since minute ventilation was not significantly different between conditions, the improvement in RR and Vt contributed to improve alveolar ventilation. This deeper breathing pattern likely arises from a combination of several factors such as a reduction of inspiratory resistance, improved respiratory mechanics [29], humidification [30] and a positive expiratory pressure effect [14, 29, 31]. Moreover, the flow and leakage dependent washout of the upper airway has been highlighted as an important factor to reduce $PaCO_2$ [13]. The mechanisms of long-term improvement are unclear and remain to be elucidated. It could be hypothesized that a better NHF-mediated humidification improved airway clearance and inflammatory status [14, 30] which in turn decreased dynamic hyperinflation and inspiratory load [32], while improving breathing pattern (which was also observed in this review) [32], and finally improved ventilation-perfusion matching [33]. The magnitude of improvement of $PaCO_2$ with NHF was relatively modest (-3 mmHg, [95% CI -4to −2]) compared to that found with high pressure and rather high backup rate NIV (−7 mmHg [CI 95% −9 to −4], recalculated data from Tables 3 and 4) [34]. This difference could in part be explained by the difference in baseline $PaCO_2$ in the study by Kohnlein et al. (about 58 mmHg) compared to that of the studies included in the present meta-analysis (< 50 mmHg). Despite this, the indirect comparison of these confidence intervals shows some degree of overlapping so that an equivalent effect cannot totally be ruled out. This is strengthened by a recent study which compared the effects of 6 weeks of NHF with 6 weeks of NIV on $PaCO_2$ and showed substantial improvement with both treatments without any significant difference between them [35]. Therefore, NHF could be relevant for hypercapnic COPD patients who do not tolerate high-pressure NIV and long-term studies comparing the effects of NHF and NIV are now warranted.

The present results also suggest that NHF did not improve SpO_2 both at short and long-term. This was also the case for long-term PaO_2. This is strengthened by a recent study which did not support the use of NHF with room air as a stand-alone therapy to oxygenate hypoxemic COPD patients who already benefit from long-term oxygen therapy [36]. Surprisingly, one short-term study reported a significant fall in TcO_2 when using NHF supplemented with an equivalent fraction of inspired oxygen compared with 2 to 4 L/min of oxygen through nasal cannula (about -4mmHg) [24]. Reassuringly, the mean TcO_2 in the NHF group remained largely within a normal range (97 mmHg (SD 24)). Nonetheless, this result raises concern about the necessity to titrate oxygen during NHF to avoid any flushing effect of the usual oxygen prescription as previously described [29].

Interestingly, long-term NHF was associated with a decrease in the rate of acute exacerbation of COPD of about 40% in the only long-term study, which assessed this outcome at 1 year. Considering the burden of exacerbations on disease progression and functional outcome [37, 38], even a 25% reduction in this relative risk, using a conservative approach based on the lower bound of the 95% CI, would still be particularly relevant. The underlying mechanisms remain to be elucidated but the implication of humidification in the management of airway secretions retention is a plausible explanation [30]. Since exacerbation and quality of life are closely related, the improvement of the former can explain the improvement of health-related quality of life with NHF (-5% [95% CI: -8 to -2]) which exceeded the minimum clinically important difference (MCID) of -4% for the SGRQ. These results are in line with those of Rea et al., who found a significant reduction in the rate of acute exacerbation and improvement in quality of life with NHF in a mixed population of COPD and bronchiectasis patients [39]. However, the 95% CI of the present estimate is relatively wide and its lower bound falls below this MCID, so a clinically trivial effect cannot be excluded.

In the context of intensive care unit, NHF is frequently reported as better tolerated (comfort and dyspnea) than the

treatment it is compared with (oxygen or NIV) [15, 16, 40]. Conversely, the results presented here, from a single study, highlight that it may be less comfortable and elicit more dyspnea than conventional oxygen in stable COPD patients [24]. This may be attributable to the initiation of a new treatment and seems to be reversible with time because long-term dyspnea was improved. Also, the choice of the NHF flow and temperature is of real concern with regards to comfort. 30 L/min and temperature below 37 °C seems to be a good compromise between efficiency in reducing $PaCO_2$ and comfort [25, 41]. Despite this, NHF was not associated with an increase in adverse event.

Finally, while the improvement in exercise capacity associated with the use of long-term NHF was not significant, its 95% CI encompassed the MCID (25 to 33 m [42]). Because of a high level of heterogeneity, the quality of evidence was downgraded to "very low" and further studies are warranted to refine this estimate.

Limitations: The main limitation of this study was the number of included studies, reducing the meta-analysis to the combination of a maximum of two studies. Major outcomes, including hospitalization rate and mortality were only assessed in one study. Moreover, the confidence in the estimates was restricted due to methodological issues, particularly because of inadequate blinding of the participants and outcome assessors. Although some outcomes such are exacerbation are most likely not influenced by the lack of blinding, the overall quality of evidence ranged from moderate to very low.

Conclusion

NHF has the potential to reduce $PaCO_2$, acute exacerbation and improve long-term health related quality of life in stable COPD patients. Although these estimates are promising, further evidence could refine them. Caution should be taken when setting up NHF in those patients with oxygen to avoid any flushing effect of oxygen. Further long-term studies are needed to confirm the present results and should now compare the effects of NHF with those from NIV.

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Declaration of interest

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Ethical approval and consent to participate

Written informed consent was not required for this study.

Authors contribution

TB, ME, CP, FEG, and GP have made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; have drafted the submitted article or revised it critically for important intellectual content; have provided final approval of the version to be published; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. CM, YC, MP, JFM, and AC have drafted the submitted article or revised it critically for important intellectual content; have provided final approval of the version to be published; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Documents disponibles en ligne, à la page de l'article sur le site de la revue

https://www.tandfonline.com/doi/abs/10.1080/15412555.2019.1672637#:~:text=There%20is%20a%20growing%20body,Pulmonary%20Disease%20(COPD)%20patients.&text=NHF%20reduced%20PaCO2%2C%20acute,life%20in%20stable%20COPD%20patients.

eAppendix 1: Detailed method.

Study registration and methodology

The protocol of this systematic review and meta-analysis was prospectively registered at PROSPERO (www.crd.york.ac.uk/prospero ; CRD: 42018103358). It has been designed according to the *Cochrane Handbook for Systematic Reviews of Interventions* (206) and reported according to the PRISMA statement.

Criteria for considering studies for this review

Types of studies

Parallel and cross-over randomized trials, included those in the format of an abstract, assessing one or more of the considered outcomes.

Type of participants

Adult patients with stable COPD (no acute exacerbation in the previous 3 weeks), of any age, diagnosed based on the individual study's criteria. Studies with a mixed population of COPD and other respiratory disease(s) could be included if the data for the participants with COPD could be extracted separately.

Type of intervention

NHF with air, or supplemental oxygen if indicated by the patient's clinical status, compared with the same gas delivered without NHF.

Type of outcome measures:

Primary outcomes:

1. Arterial carbon dioxide partial pressure measured transcutaneously ($PtcCO_2$) or by arterial blood gases ($PaCO_2$);
2. Arterial oxygen partial pressure measured transcutaneously (TcO2) or by arterial blood gases (PaO_2);
3. pH measured by arterial blood bases;
4. Quality of life (assessed either with a general or a disease-specific questionnaire);
5. Deaths;
6. Number of acute exacerbations per year;
7. Number of hospitalizations per year;

Secondary outcomes:

1. Oxygen saturation measured by pulse or transcutaneous oximetry (SpO_2 and StO_2 respectively) or by arterial blood gases (SaO_2);
2. Cardiorespiratory function (heart rate (HR); forced expired volume in 1s (FEV_1); forced vital capacity (FVC);
3. Breathing pattern (volume tidal (Vt); respiratory rate (RR); minute ventilation (MV); rapid shallow breathing index (RSBI));
4. Respiratory mechanics (gastric pressure (Pga); oesophageal pressure (Poes); transdiaphragmatic pressure (Ptdia); end-expiratory lung impedance);
5. Dyspnea assessed either during or after an exercise or at rest;
6. Exercise capacity measured either by a maximal cardiopulmonary exercise testing or field tests;
7. Objective or self-reported physical activity;

8. Comfort and patient preference;
9. Adverse events.

Search methods for identification of studies

Electronic searches

MEDLINE, CENTRAL, Science Direct, Scopus, PEDro, OpenGrey and Greylit were searched from inception up to January 2019 for relevant studies in English or French. Reference list of the included studies were also checked for eligible studies.

The following key words were used and combined using Boolean operators and a sensitivity-maximizing method: “COPD”; “pulmonary disease, chronic obstructive”; “chronic respiratory failure”; “high-flow”; “high-flow cannula”; “high-flow nasal cannula”; “nasal cannula”; “humidified high-flow”; “high-flow oxygen”; “humidification therapy”; “HFNC”; “high-flow heated and humidified oxygen”.

The search strategy for PubMed using a sensitity-maximizing searching method was adapted for the other databases:

#1 “COPD”[tiab] OR “pulmonary disease, chronic obstructive”[mh] OR “chronic obstructive pulmonary disease”[tiab] OR “chronic respiratory failure”[tiab]
#2 “high-flow”[tiab] OR “high-flow cannula”[tiab] OR “high-flow nasal cannula”[tiab] OR “nasal cannula”[tiab] OR “humidified high-flow”[tiab] OR “high-flow oxygen”[tiab] OR “humidification therapy”[tiab] OR “HFNC”[tiab] OR “high-flow heated and humidified oxygen”[tiab]
#3 “randomized controlled trial”[pt] OR “randomized controlled trial”[tiab] OR “controlled clinical trial”[pt] OR “controlled clinical trial”[tiab] OR “randomized”[pt] OR “randomized”[tiab] OR “random”[pt] OR “random”[tiab]
#4 #1 AND #2 AND #3

[tiab] denotes a word in the title or abstract.
[mh] denotes a Medical Subject Heading term.
[pt] denotes a Publication Type term.

Data collection and analysis

Details about the data collection and analysis strategy are shown in eAppendix 1.

Selection of studies

Two authors (TB, CP) independently assessed relevant studies for inclusion. Any disagreement was resolved by discussion and the intervention of a third author (GP). The level of agreement was assessed using a kappa statistic.

Data extraction and management

Two authors (TB, CP) independently extracted data on the outcome of interest using a common data extraction form. For continuous outcomes, mean (SD) change from baseline and/or mean (SD) post-treatment values for each group were recorded. When they were not available in another format, data were graphically extracted using Get Data Graph Digitizer 2.24. Skewed data were converted into mean (SD)(221, 222). The number of events was recorded for count outcomes. Study characteristics (methods, participants, intervention and outcomes) were also extracted.

Data from cross-over studies were managed according to the *Cochrane Handbook for Systematic Reviews of Interventions.*(206) Studies were grouped into the following categories with each category of studies analyzed separately: short-term studies (less than 7 days, including single treatment studies); studies of NHF during exercise; and long-term studies. In the case of studies with multiple intervention arms, the higher flow was considered for analysis. In the case of studies that measured outcomes at multiple time points, the latest period or the closest matched time point was considered for analysis.

Assessment of risk of bias in the included studies

Two authors (TB, GP) independently assessed the methodological quality of the included studies using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions.*(206) The methodological criteria included random sequence generation,

allocation concealment, blinding, incomplete outcome data, selective reporting and other potential bias. Any disagreement was resolved by discussion or the intervention of a third author (CP).

Measures of treatment effect

The effect of the treatment was estimated by mean differences (MD) or standardized mean difference (SMD) for continuous outcomes and risk ratio (RR) for counts, with their corresponding confidence intervals (CIs).

Unit of analysis issue

The unit of analysis was at the participant level. There were no cluster-randomized studies included in this systematic review.

Dealing with missing data

The impact of missing data was assessed in the "risk of bias" assessment. Original authors were contacted to obtain complementary data when necessary and analysis was performed based on available data.

Assessment of heterogeneity

Heterogeneity was assessed using the I^2 and Chi^2 statistic, considering values $I^2 \geq 50\%$ as a sign of moderate to high heterogeneity.

Assessment of reporting bias

The protocol for the systematic review stated that this would be assessed by funnel plot of 10 or more studies were available for a given meta-analysis.

Data synthesis

Meta-analysis was performed with a fixed-effect model when heterogeneity was low (< 50%), using the inverse-variance method. In the case of moderate to high heterogeneity, a random-effect model was used. RevMan 5.3.5 was used for every analysis. The quality of evidence was rated using the GRADE system. When meta-analysis was not possible, a narrative synthesis of original study data was performed.

Subgroup analysis

The protocol for the systematic review stated that subgroup analyses would be done to assess the effect low flow (10 to 20L/min) and high flow (30 or more L/min) NHF compared with control, if there were sufficient studies.

Sensitivity analysis

The protocol for the systematic review stated that sensitivity analyses would be done to assess the consistency of the results after removing high-bias studies.

Appendix 2: detailed evaluation of the risk of bias.

Risk of bias – Nagata et al. 2017		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	« Randomization was performed at Translational Research Informatics Center, Kobe, Japan, using permuted block method with block sizes of 2 and 4 »
Allocation concealment (selection bias)	Low	« Institution and patient registration will be performed using the centralized registration system following the procedure below. » complete data are available in online data supplement
Blinding : participant and personnel (performance bias)	High	« First, the subjects were not blinded to treatment, and therefore, those receiving the intervention may have overreported improvements in subjective outcomes, such as health-related QOL »
Blinding : outcome assessment (detection bias)	High	As above
Incomplete outcome data (attrition bias)	High	Intention-to-treat, flow chart According to the flow-chart, 13 patients were analysed out of the 14 patients included
Selective reporting (reporting bias)	Low	Important outcomes reported All outcomes are announced in NCT registration.
Other	Unclear	« Tomii K reports honoraria from Teijin Pharma Limited » « Primary Source of Funding: Teijin Pharma Limited » No washout period

Risk of bias – Storgaard et al. 2018		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	« In this randomized, prospective trial a total of 200 patients were included from 4 outpatient clinics in the North Jutland Region of Denmark between December 2013 and July 2015 » but no more details
Allocation concealment (selection bias)	Low	« By the use of numbered sealed envelopes containing group allocations, patients were randomly assigned to either LTOT (controls) or LTOT plus HFNC home treatment »
Blinding : participant and personnel (performance bias)	High	No placebo treatment « A randomized blinded study could have been wished for, however, blinding the patients against the ow, the heat and the humidity is not realistic »
Blinding : outcome assessment (detection bias)	High	As above
Incomplete outcome data (attrition bias)	Low	Intention-to-treat, flow-chart « The analysis population was defined as all subjects randomized to treatment and who had no major protocol deviations affecting efficacy data, giving 100% inclusion of all 200 subjects enrolled. As such, data were included on patients who discontinued the study or paused treatment and those who discontinued HFNC but stayed in the study, in the HFNC group (intention-to-treat) »
Selective reporting (reporting bias)	Unclear	All outcomes are not reported in ClinicalTrials Data are not included in the text and tables of the study

Other	Unclear	« Hans-Ulrich Hockey received remuneration from Fisher & Paykel, who also contributed equipment and some administration costs »

Risk of bias – Fraser et al. 2016		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	« After the baseline period the patient will be randomised using sealed opaque envelopes » no more information
Allocation concealment (selection bias)	Low	« The order of therapy was allocated using sequentially-numbered, sealed envelopes which were not prepared by study staff »
Blinding : participant and personnel (performance bias)	High	No placebo treatment
Blinding : outcome assessment (detection bias)	High	As above
Incomplete outcome data (attrition bias)	Low	Intention-to-treat, flow-chart
Selective reporting (reporting bias)	Low	Important outcomes reported All outcomes are announced in ANZCTR registration.
Other	High	« We studied only males thus the results seen cannot be generalised to women suffering COPD » « JFF has received a research fellowship from Queensland Health Office of Health and Medical Research. JFF received an unrestricted grant from Fisher & Paykel Healthcare in support of the current study. JFF and AC have received assistance from Fisher & Paykel Healthcare to support travel and accommodation costs to attend research meetings; neither has received honoraria or consultancy fees from Fisher & Paykel »

Risk of bias – McKinstry et al. 2018		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low	« The order of administration of the four treatments was randomized. The randomisation was computer- generated by the study statistician, who had no role in the recruitment, study visits or data collection »
Allocation concealment (selection bias)	Low	« Random allocations were sealed in sequentially numbered opaque envelopes before recruitment »
Blinding : participant and personnel (performance bias)	Unclear	« Our study was single-blinded in that although participants were blinded to the actual flow rate they received, they could feel the difference between low, medium and high flows »
Blinding : outcome assessment (detection bias)	Low	« The un-blinded investigator's role included manually counting the respiratory rate and controlling the settings on the NHF device. The blinded investigator recorded $PtCO_2$, heart rate and StO_2 from the SenTec display while seated behind a screen so that they could not see the participant or myAIRVO 2 display and wearing ear plugs to avoid hearing changes to the NHF flow-rate »
Incomplete outcome data (attrition bias)	Low	Intention-to-treat, flow-chart
Selective reporting (reporting bias)	Low	Important outcomes reported All outcomes are announced in ANZCTR registration
Other	Unclear	« The study was funded by Fisher and Paykel Healthcare New Zealand » Lack of staff calculation

Risk of bias – Nilius et al. 2013		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	« The study design consisted of a randomized crossover design » but no more details
Allocation concealment (selection bias)	Unclear	Information not available
Blinding : participant and personnel (performance bias)	High	No placebo treatment
Blinding : outcome assessment (detection bias)	High	As above
Incomplete outcome data (attrition bias)	Unclear	Information not available
Selective reporting (reporting bias)	Unclear	No full-text available No registration number available
Other	High	No full-text available "This abstract is funded by: The study was supported by TNImedical Germany"

Risk of bias – Cirio et al. 2016		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear	« we performed a randomized crossover study » but no more details
Allocation concealment (selection bias)	Unclear	Information not available
Blinding : participant and personnel (performance bias)	Unclear	Single-blind but « Another limitation is the lack of blinding, difficult to be performed using the specific device for HFNC »
Blinding : outcome assessment (detection bias)	High	Single-blind for participants
Incomplete outcome data (attrition bias)	Low	Lack of flow-chart All participants inclued were analyzed
Selective reporting (reporting bias)	High	HR and blood pressure are not reported
Other	Low	No other bias seems to be present

eAppendix 3: Secondary outcomes

Long-term effects

Two studies including 229 participants contributed data on the long-term effects of NHF (223, 224). The follow-up period for these studies ranged from 6 weeks to 12 months.

Secondary outcomes:

Blood oxygen saturation

One study was available for this outcome (total 29 patients) (223). There was no difference between NHF and control in SpO_2 (MD 0 %, 95% CI 0 to 1). The same study also reported no significant difference in SpO2 at the end of the 6MWT (MD -3 %, 95% CI -9 to 3). The quality of evidence was "very low".

Cardiorespiratory function

There was no available data with regards to heart rate (HR).

Two studies assessed forced expiratory volume in 1second (FEV_1)% (total 196 participants) (24, 25). Nagata et al. showed no significant difference in FEV_1% between groups (MD 0 L/min, 95% -2 to 1) and Storgaard et al. reported a tendency toward improvement in favor of NHF (p=0.056). Detailed data were not available on the original report and we had no answer from the authors in our initiative to get the data. The quality of evidence was "low".

One study assessed forced vital capacity (FVC) (total 29 patients) (24). There was no difference between NHF and control in FVC% (MD 0 %, 95% CI -3 to 3). The quality of evidence was "very low".

Dyspnea (mMRC scale)

Two studies that measured dyspnea used the mMRC dyspnea scale, which is measured from 0 (no dyspnea except with strenuous exercise) to 4 (too breathless to leave the house or breathless when dressing or undressing).

Meta-analysis of two studies showed statistically significant effects of nasal high flow on dyspnea (pooled MD -0.3, 95% CI -0.4 to -0.1; I^2=0%; **eAppendix 5 – Figure S1**). The quality of evidence was "moderate" as shown in the summary of findings for this comparison in **Table 2**.

Nagata et al. also assessed dyspnea during the 6MWT using the BORG scale and shown no significant difference between groups (MD -0.3, 95% CI -1 to 0.4).

Exercise capacity (six-minute walk test)

Meta-analysis of two studies showed no statistically significant effects of nasal high flow on exercise capacity (pooled MD using a random effect model: 18 m, 95% CI -9 to 46; I^2=95%; **Appendix 5 – Figure S2)**. The quality of evidence was "very low" as shown in the summary of findings for this comparison in **Table 2**.

Physical activity

One study was available for this outcome (total 29 participants) (223). There was no difference between NHF and control in step count/day (MD 233, 95% CI -9 to 475). The quality of evidence was "very low".

Adverse event

Nagata et al. reported 10 events spread over 7 patients in NHF group and 6 events spread over 6 patients in the controlled group. Event directly related to intervention included night sweat

(4 patients), nasal discharge (1 patient) and insomnia (1 patient). Among these results, there were 2 reported severe events (deemed unrelated to the intervention) spread over 2 patients in both groups. On the other hand, Storgaard et al. reported that no adverse or serious adverse event occurred throughout the follow-up period (12 months).

Other outcomes

No data were available for breathing pattern, respiratory mechanics, or comfort.

Subgroup and sensitivity analyses

There were too few studies to perform any of the planned subgroup and sensitivity analyses.

Short-term effects

Three cross-over studies including 98 participants contributed data on the short-term effects of NHF (225-227).

Blood oxygen saturation

Two studies including 78 participants contributed data on blood oxygen saturation (225, 226). Meta-analysis showed no statistically significant effects of NHF on blood oxygen saturation (pooled MD using a random effect model: 0 %, 95% CI 0 to 1; I^2=83%; **Appendix 5 – Figure S3**). The quality of evidence was "very low".

Cardiorespiratory function

Two studies including 78 participants contributed data on HR (225, 226). Meta-analysis showed no statistically significant effects of nasal high flow on heart rate (pooled MD 0 bpm, 95% CI -1 to 0; I^2=49%; **Appendix 5 – Figure S4**). The quality of evidence was "very low".

One study assessed tidal volume (Vt) (30 participants) (225) and reported a significant difference between NHF and control in favor of NHF (MD 0,1 L, 95% CI 0.4 to 1.6). The quality of evidence was “very low”.

Respiratory rate (RR) was assessed in two studies (156 participants) (225, 226). Meta-analysis showed statistically significant effects of nasal high flow on respiratory rate (pooled MD -4 cpm, 95% CI -6 to -2; I^2=0%; **Appendix 5 - Figure S5**). The quality of evidence was “low”.

Overall, minute ventilation (MV) was assessed in one study (total 30 participants) (225) which shown no significant difference between NHF and control in MV (median difference -0 L/min, 95% CI -0.3 to 0.2). The quality of evidence was “very low”.

Respiratory mechanics

There was no available data with regards Pga, Poes and Ptdia.

One study assessed end-expiratory lung impedance (225) and found a significant effect in favor of NHF (mean difference in change from baseline: 61 %, 95% CI 28 to 94). The quality of evidence was “very low”.

Dyspnea

One study was available for this outcome (total 30 participants) (225) and used a visual analogical scale (VAS) which is measured from 0 (no dyspnea) to 10 (maximum dyspnea). There was a difference between NHF and control in dyspnea. COPD patients randomized to the NHF group showed a significant increase in VAS scale (MD 1, 95% CI 0.5 to 1.5). The quality of evidence was “very low”.

Exercise capacity

See *during exercise* section.

Physical activity

No available data.

Comfort

One study was available for this outcome (total 30 participants) (225) and used a visual analogical scale (VAS) which is measured from 0 (no discomfort) to 10 (maximum discomfort. COPD patients randomized to the NHF showed a significant decrease in comfort (MD 1, 95% CI 0.3 to 1.7). The quality of evidence was “very low”.

Other outcomes

No data were available for pH, physical activity and adverse event.

Subgroup and sensitivity analyses

There were too few studies to perform any of the planned subgroup and sensitivity analyses.

eAppendix 4: During exercise effects of nasal high-flow

Primary outcomes

There was no available data for any of the primary outcomes.

Secondary outcomes

Blood oxygen saturation

COPD patients randomized to the NHF group showed a significant increase in isotime SaO2 (MD 3 %, 95% CI 2 to 4).

Dyspnea

Dyspnea was assessed using the BORG scale which is measured from 0 (no dyspnea) to 10 (maximum dyspnea). NHF significantly reduced isotime dyspnea (MD -4.5, 95% CI -6.5 to -2.5).

Exercise capacity

There was a significant difference between NHF and oxygen in endurance capacity in favor of NHF (MD 109 s, 95% CI 50 to 168).

Adverse event

The study did not report any adverse event.

eAppendix 5: supplementary figures.

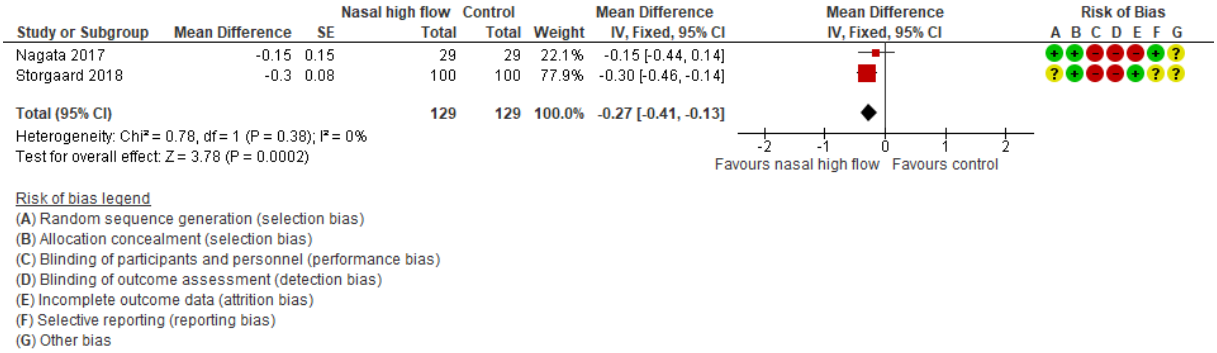

Figure S1: Long-term effects of nasal high-flow on dyspnea (dyspnea Modified Research Council scale).

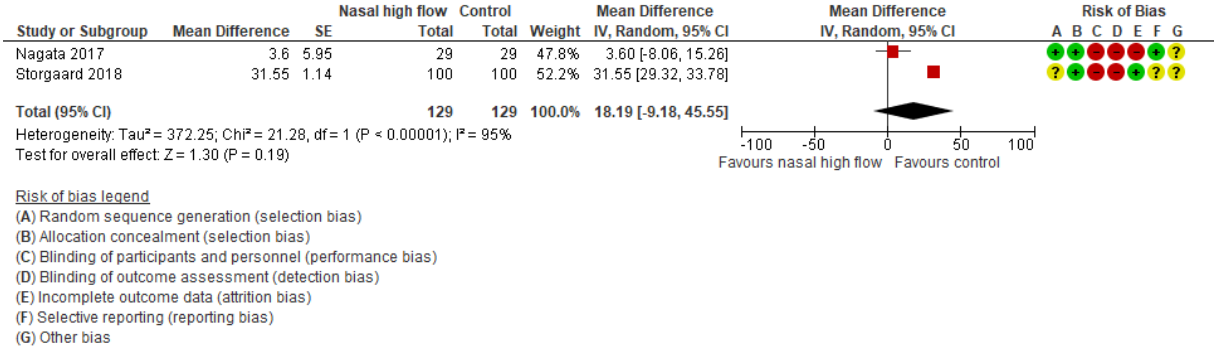

Figure S2: Long-term effects of nasal high-flow on exercice capacity (six-minute walk test, meters).

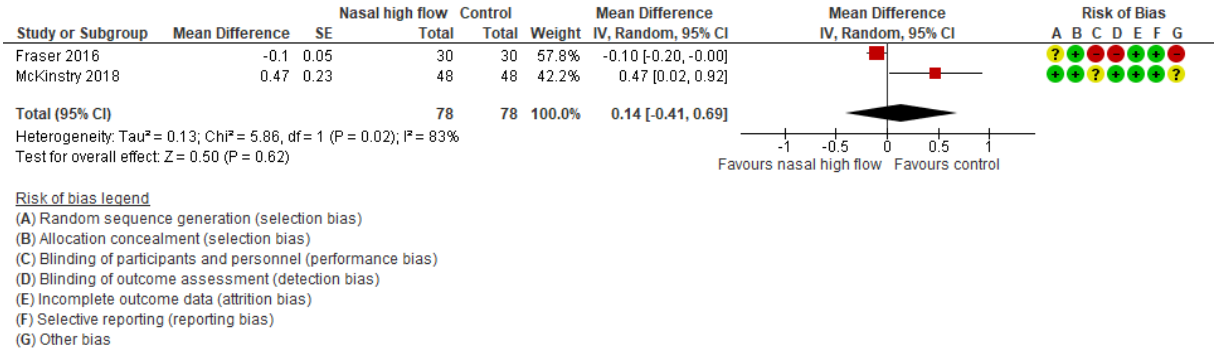

Figure S3: Short-term effects of nasal high-flow on blood oxygen saturation (%).

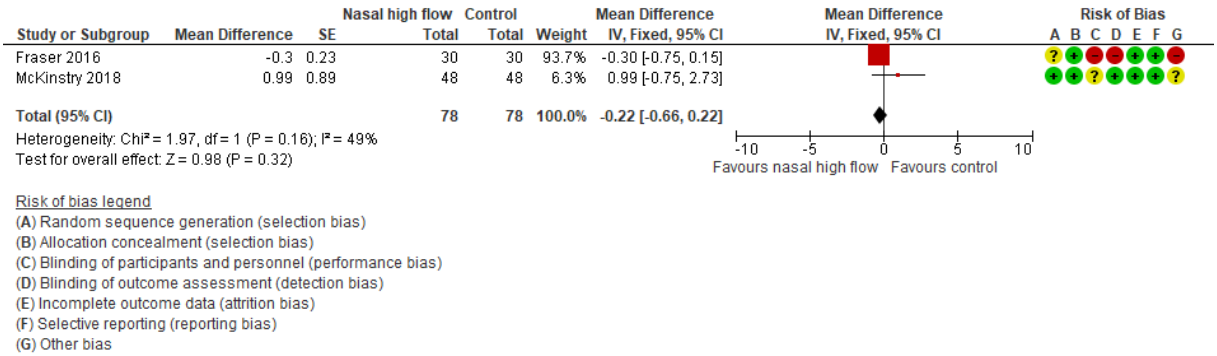

Figure S4: Short-term effects of nasal high-flow on heart rate (beat per minute).

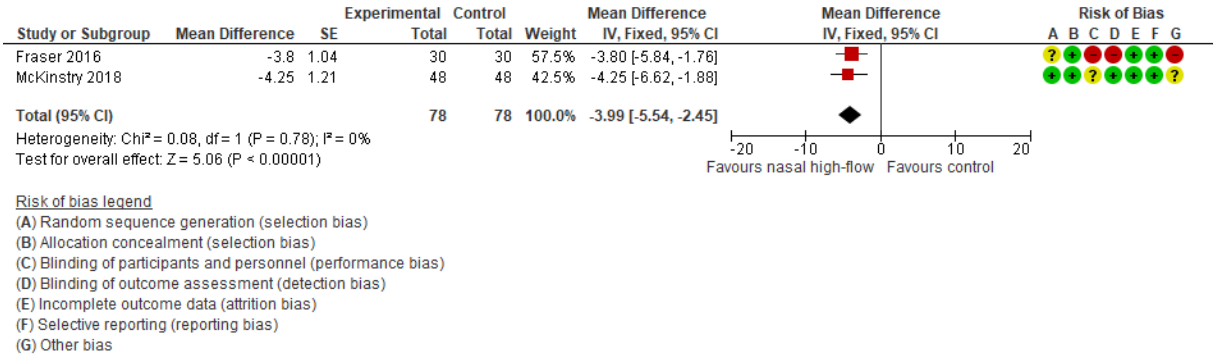

Figure S5: Short-term effects of nasal high-flow on respiratory rate (cycle per minute).

Les résultats de cette méta-analyse confirment que le haut débit nasal améliore le pattern ventilatoire des patients atteints de BPCO (à court terme) ainsi que les échanges gazeux (nottamment la PaCO2) et le risque de survenue d'une exacerbation (tous deux sur le long terme). Malgré cela, cette méta-analyse met surtout en avant que ce traitement reste peu évalué et révèle de nombreuses pistes de recherche, actuellement non explorées. Ainsi, notre méta-analyse révèle à travers une étude unique ((228)) que le haut débit nasal semble pouvoir améliorer la capacité à l'exercice en endurance de patients atteints de BPCO à l'état stable. Néanmoins, les mécanismes physiologiques sous-jacents restent inconnus. Une meilleure compréhension de ces mécanismes permettrait d'adapter au mieux les réglages du dispositif avant d'évaluer son utilisation au cours d'un programme complet de réhabilitation respiratoire. Aussi, nous venons de débuter une étude dont l'objectif est d'évaluer les effets physiologiques aigus du haut débit nasal au cours de l'effort à haute intensité et à charge constante (dont ses effets sur la charge de travail diaphragmatique et le métabolisme musculaire périphérique) chez les patients atteints de BPCO sévère à très sévère (During-exercise physiological effects of nasal high-flow in patients with chronic obstructive pulmonary disease; **NCT04014868**).

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: November 27, 2019

ClinicalTrials.gov ID: NCT04014868

Study Identification

Unique Protocol ID:	AIRVO-PHYSIO
Brief Title:	During-exercise Physiological Effects of Nasal High-flow in Patients With Chronic Obstructive Pulmonary Disease (AIRVO-PHYSIO)
Official Title:	During-exercise Physiological Effects of Nasal High-flow in Patients With Chronic Obstructive Pulmonary Disease
Secondary IDs:	

Study Status

Record Verification:	November 2019
Overall Status:	Recruiting
Study Start:	November 22, 2019 [Actual]
Primary Completion:	July 1, 2021 [Anticipated]
Study Completion:	January 1, 2022 [Anticipated]

Sponsor/Collaborators

Sponsor:	ADIR Association
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 2018-09-01 RIPH 1 Board Name: Comité de Protection des Personnes Ile De France 2 Board Affiliation: Hôpital Necker - France Phone: 0142192688 Email: cppidf2@gmail.com Address: 149 rue de Sèvres 75743 Paris Cedex 5
Data Monitoring:	No

FDA Regulated Intervention: No

Study Description

Brief Summary: Chronic obstructive pulmonary disease is a major cause of disability and mortality worldwide. This disease progressively leads to dyspnea and exercise capacity impairment. Pulmonary rehabilitation teaches chronic obstructive pulmonary disease patients to cope effectively with the systemic effects of the disease and improves exercise capacity, dyspnea and quality of life in patients with chronic obstructive pulmonary disease. However, the best training modality remains unknown. Physiological studies highlight the benefit of high intensity endurance training. However, many patients do not tolerate such a training due to ventilatory limitation and dyspnea. Therefore, a strategy to reduce dyspnea would allow a greater physiological muscle solicitation and improvement. Thus, many studies focus on means to increase exercise tolerance in patients with chronic obstructive pulmonary disease.

Nasal high flow delivers heated and humidified high flow air (up to 60 L/min) through nasal cannula providing physiological benefits such as positive airway pressure and carbon dioxide washout. It can be used in association with oxygen and offers the advantage to overtake the patient's inspiratory flow, providing a stable inspired fraction of oxygen. Nasal high flow has widely been studied in pediatric and adult intensive care units and seems better than conventional oxygen therapy and as effective as noninvasive ventilation with regards to mortality to treat hypoxemic acute respiratory failure.

More recently, nasal-high flow has been shown to improve endurance exercise capacity in patients with chronic obstructive pulmonary disease. However, the underlying physiological mechanisms have not been yet elucidated but may help to optimise the utilization of the device.

Therefore, the primary objective of this study is to assess the respiratory physiological effects nasal high-flow during-exercise in stable patients with chronic obstructive pulmonary disease.

Secondary objectives are to assess the effects nasal high-flow during-exercise on endurance capacity, respiratory drive, dynamic hyperinflation, cardiorespiratory pattern and muscular metabolism.

Detailed Description: Experimental design:

Patients referred for pulmonary rehabilitation will be approached to participate in this study. Eligible patients who agree to participate in the study and sign informed consent will perform two constant workload exercise testing the same day with either nasal high-flow or sham nasal high-flow (separated by a 1 hour rest-period) in a randomized order.

Conditions

Conditions: Chronic Obstructive Pulmonary Disease

Keywords: Chronic obstructive pulmonary disease
Exercise
Nasal high flow
Muscle

Study Design

Study Type: Interventional

Primary Purpose:	Treatment
Study Phase:	N/A
Interventional Study Model:	Crossover Assignment Single-blind randomized cross-over study.
Number of Arms:	2
Masking:	Single (Participant) The nasal high-flow device will be out of sight of the patients and will not be switched ON. The oxygen connection at the exit of the device will be obstructed. If the patient needs supplementary oxygen during-exercise, it will be provided through the fitting located just before the nasal canula (see Arms, Experimental: Nasal high-flow).
Allocation:	Randomized
Enrollment:	14 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Nasal high-flow Patients will perform a constant workload exercise testing (75% of the maximal workload achieved during a previously performed incremental cardiopulmonary exercise testing) with active nasal high-flow : Flow : 30 L/min; Temperature : 34°C; The device will be out of sight of the patient. The device allow for oxygen supplementation (fitting on the back of the device). Usual oxygen prescription (if any) will be adjusted to reach a transcutaneous oxygen saturation superior to 90%. A second fitting will be placed just before the nasal canula to allow for oxygen supplementation during the sham nasal high-flow (device turned OFF) test. Due to the cross-over design of the study, all patients will perform both interventions.	Device: Nasal high-flow See arm description.
Sham Comparator: Sham nasal high-flow Patients will perform a constant workload exercise testing (75% of the maximal workload achieved during a previously performed incremental cardiopulmonary exercise testing) with a sham nasal high-flow : The procedure will be exactly the same but the device (out of sight of the patient) will be turned OFF. Oxygen supplementation will be possible through the fitting placed just before the nasal canula. Due to the cross-over design of the study, all patients will perform both interventions.	Sham nasal high-flow See arm description.

Outcome Measures

Primary Outcome Measure:

1. Transdiaphragmatic pressure-time product using a single-use catheter with two balloons to measure gastric and esophageal pressures.

Transdiaphragmatic pressure is calculated as gastric pressure minus oesophageal pressure. The outcome will be continuously recorded during the two constant workload exercise testing. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

[Time Frame: The outcome will be continuously recorded during the two constant workload exercise testing. The 2 tests will be performed the same day for a total time frame of 3hours.]

Secondary Outcome Measure:

2. Ventilatory drive using diaphragmatic electromyogram through the same single-use catheter used for transdiaphragmatic pressure (which is provided with 6 pairs of electrodes).
   Diaphragmatic electromyography will be recorded with 6 pairs of electrodes and will be used as a surrogate for ventilatory drive. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

   [Time Frame: The outcome will be continuously recorded during the two constant workload exercise testing. The 2 tests will be performed the same day for a total time frame of 3hours.]

3. Ventilatory efficiency using indirect calorimetry
   Ventilatory efficiency will be assessed as the ratio between exercise ventilation to carbon dioxide production. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

   [Time Frame: The outcome will be continuously recorded during the two constant workload exercise testing. The 2 tests will be performed the same day for a total time frame of 3hours.]

4. Dynamic hyperinflation using the fall in during-exercise inspiratory capacity
   Maximal inspiratory maneuver will be performed every minute during the two constant workload exercise testing. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

   [Time Frame: The outcome will be recorded during the two tests. The 2 tests will be performed the same day for a total time frame of 3hours.]

5. Transcutaneous arterial carbon dioxide partial pressure using capnography.
   The outcome will be measured at the earlobe. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

   [Time Frame: The outcome will be continuously recorded during the two constant workload exercise testing. The 2 tests will be performed the same day for a total time frame of 3hours.]

6. Dyspnea during the constant workload exercise testing using modified Borg scale (0-10).
   Borg scale range from 0 (no breathlessness) to 10 (maximal breathlessness). The dyspnea will be assessed every 30sec during the constant workload exercise testing. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

   [Time Frame: The outcome will be recorded during the two tests. The 2 tests will be performed the same day for a total time frame of 3hours.]

7. Vastus lateralis muscle peripheral perfusion during exercise using near infrared spectroscopy.
   The outcome will be assessed every minute. Peripheral muscle perfusion will be assessed using the linear increase in total haemoglobin and myoglobin during a venous occlusion (20 seconds) and used as a surrogate for local blood perfusion. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

   [Time Frame: The outcome will be recorded during the two tests. The 2 tests will be performed the same day for a total time frame of 3hours.]

8. Vastus lateralis muscular peripheral oxygen extraction during exercise using near infrared spectroscopy.
   The outcome will be assessed continuously. Vastus lateralis muscle oxygen extraction will be assessed using deoxyhaemoglobin and deoxymyoglobin as a surrogate for peripheral oxygen extraction. Results will be shown at time limit and iso time (defined as time limit of the shortest test).

   [Time Frame: The outcome will be recorded during the two tests. The 2 tests will be performed the same day for a total time frame of 3hours.]

9. Endurance exercise capacity in seconds.
   Patients will perform a constant workload exercise testing at 75% of the maximal workload achieved during the incremental cardiopulmonary exercise testing.

[Time Frame: The outcome will be measured after every test. Data will be continuously collected during the tests. The 2 tests will be performed the same day for a total time frame of 3hours.]

Eligibility

Minimum Age:	18 Years
Maximum Age:	80 Years
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria:

- Age > 18years and < 80years;
- Chronic obstructive pulmonary disease Gold III-IV;
- Stable (no exacerbation) in the past 4 weeks;
- Referred for pulmonary rehabilitation (no cardiac, neurological, orthopedic, neuromuscular, psychological or psychiatric contra indication).

Non-inclusion Criteria:

- Acute exacerbation of chronic obstructive pulmonary disease between the incremental cardiopulmonary exercise testing and inclusion;
- Tracheostomy;
- Nasal high flow intolerance;
- Pregnancy or likely to be;
- Unable to consent;
- Patients under guardianship.

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Sub-Investigator: Francis-Edouard Gravier, Msc

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Citations:

Links:

Available IPD/Information:

Au-delà du programme initial de réhabilitation respiratoire, l'enjeu principal est le maintien d'une activité physique sur le long terme. En son absence, les bénéfices obtenus durant le programme initial disparaissent généralement un an après la réhabilitation (51). Les freins au maintien d'une activité physique sont multiples et ne se limitent pas aux éléments holistiques (psychologie, nutrition, motivation etc.). Ils incluent également la dyspnée, l'obstruction bronchique (en particulier la rétention de sécrétions bronchiques majorant les résistances à l'écoulement de l'air et augmentant la charge de travail ventilatoire imposée aux muscles respiratoires), l'altération des échanges gazeux ainsi que les exacerbations répétées pouvant entrainer une hospitalisation et accélérer le déclin de la fonction musculaire (68, 130, 181, 229-234). Etant donné les effets potentiels du haut débit nasal sur la dyspnée, les échanges gazeux et les exacerbations mis en avant dans notre contribution originale, ainsi que ses effets potentiels sur la clairance des voies aériennes chez les patients obstructifs (235), nous formulons l'hypothèse que le haut débit nasal institué au décours d'un programme de réhabilitation respiratoire permettrait un meilleur maintien des bénéfices acquis, 6 mois après la fin de programme. C'est à ce questionnement que le protocole **NCT03882372** (Nasal high-flow to maintain the benefits of pulmonary rehabilitation in patients with chronic obstructive pulmonary disease) mis en place au sein de notre laboratoire tente de répondre.

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: May 13, 2019

ClinicalTrials.gov ID: NCT03882372

Study Identification

Unique Protocol ID:	PPR-NHF
Brief Title:	Nasal High Flow to Maintain the Benefits of Pulmonary Rehabilitation in Chronic Obstructive Pulmonary Disease Patients (PPR-NHF)
Official Title:	Nasal High Flow to Maintain the Benefits of Pulmonary Rehabilitation in Patients With Severe to Very Severe Chronic Obstructive Pulmonary Disease - A Randomized Controlled Study
Secondary IDs:	

Study Status

Record Verification:	May 2019
Overall Status:	Not yet recruiting
Study Start:	June 1, 2019 [Anticipated]
Primary Completion:	November 1, 2021 [Anticipated]
Study Completion:	April 1, 2022 [Anticipated]

Sponsor/Collaborators

Sponsor:	ADIR Association
Responsible Party:	Sponsor
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	No
U.S. FDA-regulated Device:	No
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 2018/54 Board Name: Comité de Protection des Personnes Est I Board Affiliation: Centre hospitalier la Chartreuse Phone: 0380425485 Email: cppest1@chlcdijon.fr Address: CENTRE HOSPITALIER LA CHARTREUSE 1 BOULEVARD CHANOINE KIR - BP 23314

21033 DIJON CEDEX

Data Monitoring: No

FDA Regulated Intervention: No

Study Description

Brief Summary: Chronic obstructive pulmonary disease (COPD) is a major cause of disability and mortality worldwide. This systemic disease progressively leads to dyspnea and exercise capacity impairment. Pulmonary rehabilitation effectively improves exercise capacity, dyspnea and quality of life in patients with COPD. However, its benefits progressively fade over time due to several factors such as the lack of regular exercise activity, dyspnea, airway secretions, hematosis impairment and acute exacerbations which can lead to hospitalization and accelerated muscle wasting.

Nasal high flow (NHF) is a support used to deliver heated and humidified high flow air (up to 60 L/min) through nasal canula providing promising physiological benefits such as positive airway pressure or upper airway carbon dioxide washout. It can be used in association with oxygen and offers the advantage to overtake the patient's inspiratory flow, providing a stable inspired fraction of oxygen. Nasal high flow has widely been studied in pediatric and adult intensive care units and seems better than conventional oxygen therapy and as effective as noninvasive ventilation with regards to mortality to treat hypoxemic acute respiratory failure.

More recently, several studies have shown that long-term nasal high flow could contribute to improve exercise capacity, dyspnea, airway secretion removal, hematosis, reduced acute exacerbations and subsequent hospitalizations in patients with COPD.

Based on these results, the primary aim of this study is to assess whether long-term nasal high flow treatment can help COPD patients to better maintain their endurance capacity following a course of pulmonary rehabilitation.

Detailed Description: Experimental design:

Patients achieving their last pulmonary rehabilitation session will be approached to participate in this study.

Eligible patients who agree to participate in the study and sign informed consent will perform two baseline visit assessments:

First visit: Incremental cardiopulmonary exercise testing. Second visit:
Other baseline assessment (see outcome section), including a constant workload exercise testing at 75% of the maximal workload achieved during the incremental exercise testing.

Then, patients will then be randomized to one of the following two arms:

- Nasal high flow,
- Usual care.

After 6 months, patients will be invited to perform the same assessment as during the second baseline visit.

Conditions

Conditions: Chronic Obstructive Pulmonary Disease

Keywords: Chronic obstructive pulmonary disease
Pulmonary rehabilitation

Nasal high flow

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	N/A
Interventional Study Model:	Parallel Assignment Single blind randomized study.
Number of Arms:	2
Masking:	Single (Outcomes Assessor) Assessors will be unaware of the patient's allocation.
Allocation:	Randomized
Enrollment:	46 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Experimental: Nasal high flow Following baseline assessment, patients randomized to the nasal high flow arm will be equipped with a nasal high flow device (myAIRVO2) administrated through the Optiflow nasal canula. Flow will be set at the highest flow tolerated (20-30 L/min): initially 30 L/min, progressively decrease if not tolerated. Temperature will be set between 34-37°C according to the tolerance : initially 37°C and decreased if not tolerated. Patients will be asked to use the device 8h per day. Patients under long-term oxygen will preserve their usual flow. The usual prescribed oxygen flow will then be titrated during nasal high flow to maintain the same baseline transcutaneous oxygen saturation as their conventional oxygen therapy (≥ 90%) to prevent any oxygen dilution effect of nasal high flow.	Device: Nasal high flow See arm description.
No Intervention: Usual care Patient randomized to the control group will have no other specific intervention than their usual care. Patients under long-term oxygen will preserve their usual flow.	

Outcome Measures

Primary Outcome Measure:

1. Endurance capacity
   Patients will perform a constant workload exercise testing at 75% of the maximal workload achieved during the incremental cardiopulmonary exercise testing.

   [Time Frame: The endurance capacity will be assessed at baseline]
2. Endurance capacity
   Patients will perform a constant workload exercise testing at 75% of the maximal workload achieved during the incremental cardiopulmonary exercise testing.

[Time Frame: The endurance capacity will be assessed post-intervention (after 6months)]

Secondary Outcome Measure:

3. Quality of life: Saint George's Respiratory Questionnaire
   Quality of life will be assessed using the Saint George's Respiratory Questionnaire. The score range from 0 (worst quality of life) to 100 (optimal quality of life).

   [Time Frame: The quality of life will be assessed at baseline]
4. Quality of life: Saint George's Respiratory Questionnaire
   Quality of life will be assessed using the Saint George's Respiratory Questionnaire. The score range from 0 (worst quality of life) to 100 (optimal quality of life).

   [Time Frame: The quality of life will be assessed at post-intervention (after 6months)]
5. Quality of life: Chronic Obstructive Pulmonary Disease Assessement Test
   Quality of life will be assessed using the Chronic Obstructive Pulmonary Disease Assessement Test

   [Time Frame: The quality of life will be assessed at baseline and post-intervention for a total time frame of 6month]
6. Quality of life: Chronic Obstructive Pulmonary Disease Assessement Test
   Quality of life will be assessed using the Chronic Obstructive Pulmonary Disease Assessement Test

   [Time Frame: The quality of life will be assessed post-intervention (after 6months)]
7. Exacerbations
   The number of chronic obstructive pulmonary disease self reported exacerbations experienced by the participants during the 6 months period of follow-up will be assessed.

   [Time Frame: The number of exacerbations will be assessed for a total time frame of 6month]
8. Hospitalizations
   The number of chronic obstructive pulmonary disease related hospitalizations experienced by the participants during the 6 months period of follow-up will be assessed.

   [Time Frame: The number of hospitalizations will be assessed for a total time frame of 6month]
9. Muscle function (1) : quadriceps muscle (rectus femoris) cross-sectional area
   The quadriceps muscle thickness will be assessed using echographies.

   [Time Frame: The quadriceps muscle thickness will be assessed at baseline]
10. Muscle function (1) : quadriceps muscle (rectus femoris) cross-sectional area
    The quadriceps muscle thickness will be assessed using echographies.

    [Time Frame: The quadriceps muscle thickness will be assessed at baseline and post-intervention for a total time frame of 6month]
11. Muscle function (2) : bioimpedance
    The overall muscle function will be assessed using bioimpedance (free fat mass minus total body water)

    [Time Frame: The overall muscle function using bioimpedance will be assessed post-intervention (after 6months)]
12. Exercise capacity
    Exercise capacity will be assessed using the six minutes walk test distance.

    [Time Frame: The distance performed during the six-minute walk test will be assessed at baseline]
13. Exercise capacity
    Exercise capacity will be assessed using the six minutes walk test distance.

    [Time Frame: The distance performed during the six-minute walk test will be assessed post-intervention (after 6months)]
14. Respiratory muscle function (1) : maximal inspiratory pressure
    [Time Frame: Maximal inspiratory pressure will be assessed at baseline]
15. Respiratory muscle function (1) : maximal inspiratory pressure
    [Time Frame: Maximal inspiratory pressure will be assessed post-intervention (after 6months)]

16. Respiratory muscle function (2) : maximal expiratory pressure
[Time Frame: Maximal expiratory pressure will be assessed at baseline]

17. Respiratory muscle function (2) : maximal expiratory pressure
[Time Frame: Maximal expiratory pressure will be assessed post-intervention (after 6months)]

18. Respiratory muscle function (3) : sniff test
[Time Frame: Sniff test will be assessed at baseline]

19. Respiratory muscle function (3) : sniff test
[Time Frame: Sniff test will be assessed post-intervention (after 6months)]

20. Parasternal electromyogram
Parasternal electromyogram will be used to assess central output during maximal inspiratory and expiratory pressure measurement as during the sniff test. Moreover, parasternal electromyogram will be assessed both at rest and during nasal high flow (30L/min, 34°C).

[Time Frame: Parasternal electromyogram will be assessed at baseline]

21. Parasternal electromyogram
Parasternal electromyogram will be used to assess central output during maximal inspiratory and expiratory pressure measurement as during the sniff test. Moreover, parasternal electromyogram will be assessed both at rest and during nasal high flow (30L/min, 34°C).

[Time Frame: Parasternal electromyogram will be assessed post-intervention (after 6months)]

22. Physical activity (1) : steps per day
The number of steps per day will be recorded over a course of 14 week days using an activity monitor.

[Time Frame: Steps per day will be assessed during 14 days following inclusion]

23. Physical activity (1) : steps per day
The number of steps per day will be recorded over a course of 14 week days using an activity monitor.

[Time Frame: Steps per day will be assessed during 14 days after 6months of intervention]

24. Physical activity (2) : time spent during activities superior to 3 metabolic equivalent per day
The time spent during activities superior to 3 metabolic equivalent per day will be over a course of 14 week days

[Time Frame: The time spent during activities superior to 3 metabolic equivalent per day will be assessed 14 days following inclusion]

25. Physical activity (2) : time spent during activities superior to 3 metabolic equivalent per day
The time spent during activities superior to 3 metabolic equivalent per day will be over a course of 14 week days

[Time Frame: The time spent during activities superior to 3 metabolic equivalent per day will be assessed during 14 days after 6months of intervention]

26. Quality of sleep (1) : Visual Analogue Scale
The quality of sleep will be assessed using a aVisual Analogue Scale (ranging from 0 to 10 with 10 indicating higher sleep quality).

[Time Frame: The quality of sleep using a Visual Analogue Scale will be assessed at baseline]

27. Quality of sleep (1) : Visual Analogue Scale
The quality of sleep will be assessed using a aVisual Analogue Scale (ranging from 0 to 10 with 10 indicating higher sleep quality).

[Time Frame: The quality of sleep using a Visual Analogue Scale will be assessed post-intervention (after 6months)]

28. Quality of sleep (2) : pittsburgh scale
The quality of sleep will be assessed using the pittsburgh scale which has been validated to assess sleep quality. The scale range from 0 (major sleep difficulties) to 21 (no difficulty).

[Time Frame: The quality of sleep using the pittsburgh scale will be assessed at baseline]

29. Quality of sleep (2) : pittsburgh scale
The quality of sleep will be assessed using the pittsburgh scale which has been validated to assess sleep quality. The scale range from 0 (major sleep difficulties) to 21 (no difficulty).

[Time Frame: The quality of sleep using the pittsburgh scale will be assessed post-intervention (after 6months)]

30. Adherence to treatment : days of utilization during the follow-up
The data will be retrieved from the nasal high flow device

[Time Frame: The number of days that the nasal high flow device was used throughout the follow-up will be assessed post-intervention in the nasal high flow arm for a total time frame of 6 months]

31. Adherence to treatment : hours of utilization per day
The data will be retrieved from the nasal high flow device

[Time Frame: The number of hours of utilization per day throughout the follow-up will be assessed post-intervention in the nasal high flow arm for a total time frame of 6 months]

Eligibility

Minimum Age:	18 Years
Maximum Age:	80 Years
Sex:	All
Gender Based:	No
Accepts Healthy Volunteers:	No
Criteria:	Inclusion Criteria:

- Chronic obstructive pulmonary disease stage III to IV;
- With or without long-term oxygen therapy;
- Having completed a course of pulmonary rehabilitation within the last 4 weeks (at least 18 sessions).

Exclusion Criteria:

- Did not complete a course of pulmonary rehabilitation;
- Using noninvasive ventilation or constant positive airway pressure treatment;
- Tracheostomy;
- Nasal high flow intolerance;
- Pregnancy or likely to be;
- Unable to consent;
- Patients under guardianship.

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Available IPD/Information:

III.4. Discussion et conclusion de la troisième partie

Les enjeux autour de la réhabilitation respiratoire sont nombreux. Afin d'élargir l'offre de réhabilitation, notamment pour les patients les plus sévères, il est nécessaire de poursuivre les recherches afin de faciliter leur évaluation physiologique, par exemple en utilisant des tests de terrain, plus proches des activités quotidiennes, ainsi que de démontrer la valeur ajoutée des programmes de réhabilitation utilisant des technologies de télécommunication avancées. Cela pourrait permettre aux patients les plus sévères, trop peu considérés pour une réhabilitation au domicile, de bénéficier d'un programme adapté avec des niveaux de supervision et de sécurité similaires à ceux proposés en centre de réhabilitation.

Ainsi, une revue systématique et méta-analyse menée sur le sujet montre que l'utilisation des technologies de santé pour encadrer la réhabilitation respiratoire pourrait être une alternative efficace à la réhabilitation respiratoire réalisée en centre. En effet, nous avons montré que cette modalité de réhabilitation est efficace pour améliorer la capacité à l'exercice, l'activité physique, l'auto-gestion et probablement la qualité de vie comparé à l'absence de réhabilitation. De plus, elle a des effets probablement similaire à la réhabilitation respiratoire en centre sur ces mêmes critères d'évaluation. Enfin, la réhabilitation à domicile guidée par les technologies de santé est similaire ou supérieure à la réhabilitation à domicile conventionnelle pour améliorer la qualité de vie, la dyspnée fonctionnelle ainsi que la qualité de vie. La principale force de ce travail réside dans sa recherche extensive de la littérature (incluant les données non publiées). Malheureusement, peu d'études ont contribué à chacune des méta-analyses réalisées et les estimations des effets de cette intervention restent à affiner. De plus, la qualité méthodologique des études inclues limite la confiance à accorder à ces estimations. Ainsi, d'autres travaux sont nécessaires pour confirmer les résultats retrouvés. Ceux-ci

devraient plus particulièrement évaluer l'impact de cette intervention sur du plus long terme et notamment comparer le rapport coût-efficacité associé à l'utilisation de telles technologies en comparaison à la réhabilitation à domicile, particulièrement lorsqu'elle considère l'utilisation de ressources minimales (184, 204). Enfin, l'intérêt de ces outils pour favoriser le maintien des acquis après le programme de réhabilitation est une piste encore très peu explorée et qui nécessite davantage d'investigations (86, 87).

D'autre part, de nouveaux outils, tels que le haut débit nasal, nécessitent d'être explorés afin de déterminer leur place dans la prise en charge des patients adressés en réhabilitation respiratoire. Une revue systématique et méta-analyse que nous avons menée sur cette thématique retrouve une amélioration du pattern ventilatoire lorque les patients utilisent le dispositif ainsi qu'une amélioration des échanges gazeux (particulièrement la PaCO2) et du risque de survenue d'une exacerbation, tous deux sur le long terme. Malgré cela, ce travail souligne surtout le manque de données sur le sujet à ce jour. Bien que la fiabilité des estimations retrouvées dans les méta-analyses soient à considérer avec prudence (faible nombre d'études, qualité méthodologique limitant la confiance dans ces estimations), le haut débit nasal pourrait représenter un adjuvant dont les bénéfices physiopathologiques et cliniques doivent être évalués dans le contexte de la réhabilitation respiratoire. En particulier, ses effets à l'exercice ont été peu évalués. Par ailleurs, son impact potentiellement positif sur les exacerbations (période durant laquelle l'atteinte musculaire périphérique est majorée (234, 236)), pourrait, de façon indirecte (à travers une prévention du déclin de la fonte musculaire), permettre un meilleur maintien des acquis sur le long terme après un programme de réhabilitation respiratoire. Ces deux pistes sont actuellement explorées au sein de notre laboratoire.

Conclusion générale

La réhabilitation respiratoire est une intervention efficace pour lutter contre les conséquences systémiques et les principaux symptômes de la BPCO mais les défis qui l'entourent sont nombreux :

- difficultés d'accès aux centres d'évaluation et de réhabiltiation ;
- optimisation des effets du programme ;
- stratégie de maintien des acquis.

Au cours de cette thèse, nous avons abordé deux problématiques majeures. La première concerne les difficultés d'accès aux programmes dans la mesure où très peu de patients en bénéficient.

Ainsi, dans l'objectif d'optimiser l'accès aux programmes de réhabilitation, nous avons pu constater 1) que le test stepper de six minutes peut être utilisé pour prescrire l'entrainement à l'exercice en endurance, particulièrement pour les patients présentant une forme légère à modérée de BPCO, mais pas pour prescrire le renforcement musculaire ; 2) que l'utilisation d'un dispositif de telemonitoring pour envisager un programme de réhabilitation respiratoire à domicile offrant un niveau de supervision équivalent à la réhabilitation en centre est faisable, valide et accepté par les participants ; 3) que la dysfonction cognitive est très fréquente parmi les patients adressés en réhabilitation respiratoire mais qu'elle pourrait s'améliorer au décours du programme et ne semble pas influencer la capacité à utiliser un système de telemonitoring.

Une seconde problématique majeure concerne la modalité optimale de réentrainement. Bien que l'entrainement à haute intensité semble particulièrement bénéfique, cette modalité est souvent mal tolérée par les patients en raison de leur handicap ventilatoire. Ainsi, différents

outils pourraient être utilisés afin de soulager le travail ventilatoire et permettre une sollicitation musculaire plus importante, potentialisant de ce fait les effets de l'entrainement à l'exercice. Dans ce cadre, notre travail a permis de démontrer 1) que l'utilisation de la ventilation non invasive au cours de l'effort n'améliore pas la performance des patients en raison de limitations technologiques du ventilateur ; 2) que la stimulation électrique excito-motrice réalisée à domicile en plus d'un programme de réhabilitation respiratoire n'apporte pas davantage de bénéfices chez les patients présentant une BPCO sévère à très sévère ; 3) que la stimulation électrique nerveuse transcutanée ne semble pas améliorer la performance à l'effort de patients présentant une BPCO sévère à très sévère.

Enfin, après avoir accédé et tiré bénéfice du programme de réhabilitation respiratoire, l'enjeu majeur reste le maintien des acquis sur le long terme. En ayant montré que le haut débit nasal pouvait améliorer les échanges gazeux et réduire le risque de survenue des exacerbations (connues pour accélérer le déclin de la fonction musculaire), nous faisons l'hypothèse que cette stratégie pourrait être efficace pour maintenir les effets positifs de la réhabilitation sur le long terme. Cette piste de recherche est actuellement en cours d'exploration au sein de notre laboratoire.

Les recherches futures devraient permettre de valider un modèle décentralisé de réhabilitation respiratoire afin d'élargir l'offre à un nombre plus important de patients. Plus particulièrement, les tests de terrain réalisables en pratique de ville ou au domicile des patients devraient plus largement être étudiés dans l'objectif de prescrire le réentrainement dans un cadre sécurisé pour une majorité des patients. La place de la téléréhabilitation dans l'offre de soins (confirmation de son équivalence vis-à-vis de la réhabiltiation en centre et de sa supériorité vis-à-vis de la réhabilitation conventionnelle à domicile) mérite également

davantage d'évaluations. D'autre part, les outils actuels et les nouveaux outils (dont le haut débit nasal) pourraient permettre d'optimiser les effets du programme en soulageant la dyspnée et en favorisant la stimulation musculaire. Il est certainement nécessaire de mieux cibler les patients y répondant. Enfin, la place de ces outils dans le maintien sur le long terme des bénéfices acquis au cours du programme est également une piste de recherche à explorer.

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Curriculum Vitae

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INFORMATIONS PERSONNELLES

Date et lieu de naissance : 03/05/1989 à Louviers, Eure (27)
Nationalité : Française
Situation familiale : Pacsé, 2 enfants
Permis B

EXPERIENCE PROFESSIONNELLE

- **Avril 2020 :** relecteur pour la Haute Autorité de Santé.
  - Réponses rapides dans le cadre du Covid-19 – Mesures et précautions essentielles pour le Masseur-Kinésithérapeute auprès des patients à domicile. Validée par le Collège le 16 avril 2020
  - Réponses rapides dans le cadre du Covid-19 – Prise en charge des patients post-COVID-19 en Médecine Physique et de Réadaptation (MPR), en Soins de Suite et de Réadaptation (SSR), et retour à domicile. Validée par le Collège le 16 avril 2020
  - Réponses rapides dans le cadre du Covid-19 – Prise en charge précoce de Médecine Physique et de Réadaptation (MPR) en réanimation, en soins continus ou en service de rééducation post-réanimation (SRPR)

- **Septembre 2018 :** expertise protocole PHRIP 2018 – DGOS Innovacs – Ministère des Affaires Sociales et de la santé.

- **Octobre 2017 :** expertise protocole PHRIP 2017 – DGOS Innovarc – Ministère des Affaires Sociales et de la Santé.

- **Mars 2012 - :** Conseiller médico-technique, exercice salarié à mi-temps, ADIR Association – Hôpital de Bois-Guillaume, Rouen.

- Réhabilitation respiratoire.
- Pathologies concernées : BPCO, IRC, mucoviscidose, asthme etc.
- Conception et participation à des protocoles de recherche clinique (réentrainement sous ventilation non invasive, télémédecine, évaluation de tests de terrain, électrostimulation).
- Exercice à temps plein à partir de Mai 2014 ; activité orientée à 20% de clinique et 80% de temps de recherche.

- **Juillet 2010 à Mai 2014 :** Exercice salarié à mi-temps, CHUR de Rouen – Service de réanimation chirurgicale, Rouen.
- Kinésithérapie respiratoire de patients adultes, ventilés ou non, en post-opératoire de chirurgie thoracique/abdominale.
- Pathologies : antécédents respiratoire (BPCO, SAS, SOH, NM, IRC) décompensée ou à risque de décompensation.
- Conception et participation à des protocoles de recherche clinique (cycloergomètre dans le sevrage de la ventilation de mécanique, entrainement en force des muscles inspirateurs chez le patient intubé).

- **Juillet 2010 à Février 2012** : Exercice libéral à mi-temps, Saint Etienne du Rouvray.

- **Décembre 2011 - :** Membre de la Société de Kinésithérapie de Réanimation.

- **Juillet 2010 - :** Association Union des Kinésithérapeutes Respiratoire (UKR), Rouen.
- Juillet 2010 - : Membre de l'association.
- Octobre 2011 - : Membre actif du bureau.
- Octobre 2012 - : Chargé de formation et organisateur des Tables rondes de l'UKR (renouvellement des formations, mise en place de nouvelles actions de formation dont certaines en partenariat avec le CHU de Rouen ; réalisation des dossiers FIF-PL et réalisation du dossier d'enregistrement pour l'OGDPC)

FORMATION INITIALE

- **Juin 2010 : Diplôme d'état de masseur-kinésithérapeute**, IFMK Rouen.

FORMATION CONTINUE

- **Janvier 2020 :** Formation au financement et management des projets de recherche, organisée par l'EdNBISE, par Mme S. VANDER EECKEN et Mr D. HONORE, Mont Saint Aignan, France.

- **Septembre 2019 :** 2èème Congrès de l'European Respiratory Society, Madrid, Espagne.

- **Mars 2019 :** Formation à l'animation de réunion, organisée par l'EdNBISE, par Mr LANCESTRE Antoine, Mont Saint-Aignan, France.

- **Février 2019 :** 7ème Journées Francophones de Kinésithérapie, SFP, Montpellier, France.

- **Septembre 2018 :** 26ème Congrès de l'European Respiratory Society, Paris, France.

- **Juillet 2018 :** Formation aux méthodes biostatistiques pour l'analyse des données, organisée par l'EdNBISE, par Me BERARD Caroline, Mont Saint-Aignan, France.

- **Mars 2018 :** 12ème Journées Francophones ALVEOLE, SPLF, Nantes.

- **Septembre 2017 :** Ateliers EFX, par Mrs les Pr RICHARD et Pr COSTES, organisé par la SPLF et le groupe Alvéole, Paris.

- **Années Universitaire 2017- : Thèse de 3ème cycle, Science Médicale,** Université de Rouen
  - **Unité d'Accueil 3830 :** Groupe de Recherche sur le Handicap Ventilatoire.

- **Aout 2017 :** ICH Good Clinical Practice E6 (R2). Formation en ligne, plateforme Global Health Training Center.

- **Janvier 2017 :** 21ème Congrès de Pneumologie de Langue Française, Marseille.

- **Mars 2016 :** 11ème Journées Francophones ALVEOLE, SPLF, Lyon.

- **Janvier 2016 :** 20ème Congrès de Pneumologie de Langue Française, Lille.

- **Année Universitaire 2014-2015 : Master 2 Ingénierie de la Rééducation, du Handicap et de la Performance Motrice (IRHPM)**, mention Bien, Université de Picardie Jules Verne, S2I, Amiens.

- **Septembre 2015 :** 25ème congrès de l'European Respiratory Society, Amsterdam, Pays-Bas.

- **Janvier 2015 :** 19ème Congrès de Pneumologie de Langue Française, Lille.

- **Mai 2014 :** Case-based introduction to biostatistics. Formation en ligne, plateforme COURSERA, Université Johns Hopkins, Baltimore.

- **Mai 2014 :** Le muscle en réanimation, du dysfonctionnement à la réhabilitation, Société de Kinésithérapie de Réanimation, Paris.

- **Mars 2014 :** 10ème Journée Alvéole, Nantes.

- **Janvier 2014 :** 18ème Congrès de Pneumologie de Langue Française, Marseille.

- **Novembre 2013 :** Actualités en ventilation 2013, Clinique Universitaire Saint Luc, Bruxelles.

- **Janvier 2013 :** 17ème Congrès de Pneumologie de Langue Française, Lille.

- **Octobre 2012 : Diplôme Universitaire d'éducation des patients**, Université de Rouen, Rouen.

- **Septembre 2012 :** Ventilation mécanique invasive et non invasive, organisée par la SKR, par M. ROESELER Jean, Bruxelles.

- **Novembre 2011 à Juin 2012 : Diplôme Inter-Universitaire de spécialité en kinésithérapie, mention kinésithérapie respiratoire et cardio-vasculaire**, Université Paris Descartes V, Paris.

- **Janvier 2012 :** 16ème Congrès de Pneumologie de Langue Française, Lyon.

- **Octobre 2011 :** Formation des kinésithérapeutes à la réhabilitation respiratoire, organisée par l'UKR, par M. SELLERON Bertrand, Bois-Guillaume.

- **Juin 2011 :** La prise en charge des patients handicapés ventilatoires, organisé par l'EEAP Tony Larue, par M. le Pr. CUVELIER Antoine et collaborateur, Le Grand Quevilly.

- **Janvier à Avril 2011-2014 :** Tables rondes de l'Union des Kinésithérapeutes Respiratoires, Bois-Guillaume.

- **Janvier 2011 :** 15ème Congrès de Pneumologie de Langue Française, Lille.

- **Décembre 2010 :** Actualités en Ventilation Non Invasive et kinésithérapie respiratoire, par M. le Pr. MUIR Jean-François et collaborateur, Isneauville.

- **Novembre 2010 :**

  - Journées Lyonnaises Paramédicales Réanimation, Lyon.
  - Formation Power Plate, Paris.
  - Le masseur-kinésithérapeute : acteur clé du dépistage de la BPCO, par M. le Pr. MUIR Jean-François et collaborateur, Rouen.

- **Octobre 2010 :** Actualisation de la pratique de kinésithérapie respiratoire du bilan diagnostic aux techniques, par M. GOUILLY Pascal, Bois-Guillaume.

ACTIONS DE FORMATION / CONFERENCES SUR INVITATIONS

- **Septembre 2019 :** Bonnevie T ; Gravier FE ; Prieur G ; Combret Y ; Debeaumont D ; Patout M ; Lamia B ; Viacroze C ; Muir JF ; Médrinal C ; Cuvelier A. Effects of lumbar transcutaneous electrical nerve stimulation in patients with COPD – A randomized double-blind cross-over study. 27ème Congrès de l'European Respiratory Society (**Communication Orale**), Madrid, Espagne.

- **Mars 2019 :** Formation des kinésithérapeutes à la réhabilitation respiratoire, UKR, Rouen.

- **Février 2019 :** Intervention lors des 7èmes Journées Francophones de Kinésithérapie sur thème : « La place de l'électrostimulation dans l'insuffisance respiratoire », Société Française de Kinésithérapie, Montpellier.

- **Avril 2018 :** Formation des kinésithérapeutes à la réhabilitation respiratoire, UKR, Rouen.

- **Février 2018 :** Intervention lors du CIFPK 2018 sur le thème : « Quels tests de terrain pour évaluer mon patient ? », Rouen.

- **Juin 2016 :** Formation des kinésithérapeutes à la réhabilitation respiratoire, UKR, Rouen.

- **Janvier 2016 :** Intervention lors du 20ème Congrès de Pneumologie de Langue Française, Atelier 22 « Réentrainement sous VNI de la théorie à la pratique », SPLF, Lille.

- **Novembre 2015 :** Intervention lors de la formation « Formation des kinésithérapeutes à l'utilisation de la VNI », sur le thème de « L'utilisation de la ventilation non invasive pour l'activité physique des patients », Groupe de Travail en Kinésithérapie (issu de la SPLF), Rouen.

- **Novembre 2014 :** Intervention orale lors de la 3ème journée nationale de la SKR, sur le thème « Les muscles ventilatoires : de la réanimation à la réhabilitation », Société de Kinésithérapie de Réanimation, Paris.

- **Mai 2014 :** Intervention orale lors de la formation « Le muscle en réanimation, du dysfonctionnement à la réhabilitation », sur le thème de « L'IMT en pratique : évaluation du diaphragme et moyens techniques de préventions et de rééducation », Société de Kinésithérapie de Réanimation, Paris.

- **Janvier 2014 :** Table ronde de l'UKR sur le thème de : « La réhabilitation respiratoire, c'est quoi ? », ADIR Association, hôpital de Bois-Guillaume.

MISSIONS D'ENSEIGNEMENT UNIVERSITAIRE

- **Juillet 2010 - :** Institut de formation en masso-kinésithérapie, CHUR Rouen, Rouen.
- Juillet 2010 - : Directeur de mémoire, à orientation recherche depuis 2017.
- Septembre 2012 - : Partenaire de formation dans le module 7 cardio-respiratoire.
  - Travaux Dirigés : Techniques de drainage bronchique
  - Travaux Dirigés : La réhabilitation respiratoire
  - Cours magistral : Rééducation des pathologies du contenant
  - Cours magistral : Utilisation des bases de données scientifique – Evidence Based Practice et méthodologie de la recherche documentaire.
  - Travaux Dirigés : Utilisation des bases de données scientifique – Evidence Based Practice et méthodologie de la recherche documentaire.
  - Evaluation : Projets de mémoires.
  - Evaluation : Soutenance critique d'articles scientifiques.
- Septembre 2013-2016 : Coordinateur du module 7 versant rééducation.
- Juin 2018- : Jury du Diplôme d'Etat de Masseur-Kinésithérapeute.

PUBLICATIONS DANS DES REVUES A COMITE DE LECTURE

- Combret Y ; Médrinal C ; Bonnevie T ; Gravier FE ; Le Roux P ; Lamia B ; Prieur G ; Reychler G (2020). Clinimetric evaluation of muscle function tests for individuals with cystic fibrosis: A systematic review. J Cyst Fibros [Accepted]
- Bonnevie T ; Médrinal C ; Combret Y ; Debeaumont D ; Lamia B ; Muir JF ; Cuvelier A ; Prieur G ; Gravier FE (2020). Mid-term effects of pulmonary rehabilitation on cognitive function in people with severe chronic obstructive pulmonary disease. Int J COPD 15:1111-21

- Médrinal C ; Combret Y ; Hilfiker R ; Prieur G ; Aroichane N ; Gravier FE ; Bonnevie T ; Contal O ; Lamia B (2020). ICU Outcomes Can Be Predicted by Non Invasive Muscle Evaluation: A Meta-Analysis. ERJ [Accepted]

- Bonnevie T ; Gravier FR ; Fresnel E ; Kerfourn A ; Médrinal C ; Prieur G ; Combret Y ; Muir JF ; Cuvelier A ; Debeaumont D ; Reychler G ; Patout M ; Viacroze C (2020). NIV is not adequate for high intensity endurance exercise in COPD. J Clin Med 9(4):1054

- Prieur G ; Combret Y ; Médrinal C ; Arnol N ; Bonnevie T ; Gravier FE ; Quieffin J ; Lamia B ; Reychler G ; Borel JC (2020). Energy conservation technique improves dyspnea when patients with severe COPD climb stairs: a randomised crossover study. Thorax [Accepted]

- Bonnevie T ; Elkins M (2019). Chronic obstructive pulmonary disease. J Physiother 66(1):3-4

- Gravier FE ; Bonnevie T ; Cuvelier A (2019). Reply : Prehabilitation versus standard care – What impact on complications ? J Thor Card Vasc Surg [Accepted]

- Bonnevie T ; Elkins M ; Paumier C ; Médrinal C ; Combret Y ; Patout M ; Muir JF ; Cuvelier A ; Gravier FE ; Prieur G (2019). Nasal high flow for stable patients with chronic obstructive pulmonary disease : a systematic review and meta-analysis. COPD 16(5-6):368-77

- Bonnevie T ; Gravier FE ; Prieur G ; Combret Y ; Debeaumont D ; Patout M ; Lamia B ; Muir JF ; Médrinal C ; Cuvelier A (2019). Lumbar Transcutaneous Electrical Nerve Stimulation to improve exercise performance in COPD patients. Eur Respir J 54(6)

- Comes J ; Prieur G ; Combret Y ; Gravier FE ; Bonnevie T ; Médrinal C (2019). Changes in cycle-ergometer performance during pulmonary rehabilitation predict COPD exacerbation. COPD 16(3-4):308

- Prieur G ; Médrinal C ; Combret Y ; Dupuis Lozeron E ; Bonnevie T ; Gravier FE ; Quieffin J ; Lamia B ; Borel JC ; Reychler G (2019). Nasal high-flow does not improve exercise tolerance in COPD patients recovering from acute exacerbation: A randomized cross-over study. Respirology 24(11):1088-94

- Comes J ; Prieur G ; Combret Y ; Gravier FE ; Gouel B ; Quieffin J ; Lamia B ; Bonnevie T ; Médrinal C (2019). Changes in cycle-ergometer performance during pulmonary rehabilitation predict COPD exacerbation. COPD 16(3-4):261-5

- Gravier FE ; Bonnevie T ; Boujibar F ; Médrinal C ; Prieur G ; Combret Y ; Muir FJ ; Cuvelier A ; Baste JM ; Debeaumont D (2019). Effect of ambulatory prehabilitation on ventilatory efficiency in patients awaiting lung resection surgery for Non-Small Cell Lung Cancer: a cohort study. J Thor Card Vasc Surg 157(6):2504-2512 e1

- Bonnevie T ; Allingham M ; Prieur G ; Combret Y ; Debeaumont D ; Patout M ; Cuvelier A ; Viacroze C ; Muir JF ; Médrinal C ; Gravier FE (2019). The six-minute stepper test is related to muscle strength but cannot substitute for the one repetition maximum to prescribe strength training in patients with COPD. Int J COPD 14:767-774

- Prieur G ; Combret Y ; Bonnevie T ; Gravier FE ; Robledo Quesada A ; Quieffin J ; Lamia B ; Médrinal C (2019). Functional electrical stimulation changes muscles oxygenation in patients with chronic obstructive pulmonary disease during moderate-intensity exercise : a secondary analysis. COPD 16(1):30-36

- Bonnevie T ; Gravier FE ; Elkins M ; Dupuis J ; Prieur G ; Combret Y ; Viacroze C ; Debeaumont D ; Quieffin J ; Bouchra L ; Patout M ; Cuvelier A ; Muir JF ; Médrinal C ; Tardif C (2019). People undertaking pulmonary rehabilitation are willing and able to provide accurate data via a remote pulse oximetry system: a multicentre observational study. J Physiother 65(1):28-36

- Boujibar F ; Bonnevie T ; Debeaumont D ; Bubenheim M ; Cuvelier A ; Peillon C ; Gravier FE ; Baste JM (2018). Impact of prehabilitation on morbidity and mortality after pulmonary lobectomy by minimally invasive surgery: a cohort study. J Thor Dis 10(4):2240-8

- Médrinal C ; Combret Y ; Prieur G ; Robledo Quesada A ; Bonnevie T ; Gravier FE ; Dupuis Lozeron E ; Frenoy E ; Contal O ; Lamia B (2018). Comparison of exercise intensity during four early rehabilitation techniques in sedated and ventilated patients in ICU: a randomized cross-over trial. Crit Care 22(1):110

- Médrinal C ; Prieur G ; Combret Y ; Robledo Quesada A ; Debeaumont D ; Bonnevie T ; Gravier FE ; Dupuis Lozeron E ; Quieffin J ; Contal O ; Lamia B (2018). Functional electrical stimulation – A new therapeutic approach to enhance exercise intensity in chronic obstructive pulmonary disease patients : a randomised controlled cross-over trial. Arch Phys Med Rehab 99(8):1454-61

- Bonnevie T ; Gravier FE ; Debeaumont D ; Viacroze C ; Muir JF ; Cuvelier A ; Netchitailo M ; Roy AL ; Quieffin J ; Marques MH ; Médrinal C ; Dupuis J ; Tardif C (2018). Home-based neuromuscular electrical nerve stimulation as an add-on to pulmonary rehabilitation does not provide further benefits in patients with chronic obstructive pulmonary disease: A multicenter randomized trial. Arch Phys Med Rehab 99(8):1462-70

- Médrinal C ; Prieur G ; Combret Y ; Robledo Quesada A ; Bonnevie T ; Gravier FE ; Frenoy, E ; Contal O ; Lamia B (2018). Reliability of respiratory pressure

measurements in ventilated and non-ventilated patients in ICU : an observational study. Ann Intensive Care 8(1):14

- Bonnevie T ; Gravier FE ; Cuvelier A ; Debeaumont D (2018). Six-minute stepper test to set pulmonary rehabilitation intensity in patients with COPD. COPD 15(1):91-2

- Bonnevie T ; Gravier FE ; Ducrocq A ; Debeaumont D ; Viacroze C ; Cuvelier A ; Muir JF ; Tardif C (2017). Exercise testing in patients with diaphragm paresis. Respiratory physiology & Neurobiology 248:31-5

- Bonnevie T ; Gravier FE ; Leboullenger M ; Médrinal C ; Viacroze C ; Cuvelier A ; Muir JF ; Tardif C ; Debeaumont D (2017). Six-minute stepper test to set pulmonary rehabilitation intensity in patients with COPD – A retrospective study. CPOD 14(3):293-7

- Gravier FE ; Bonnevie T ; Debeaumont D ; Viacroze C ; Tardif C ; Muir JF (2017). Programme d'éducation thérapeutique destiné aux patients atteints de BPCO dans le cadre d'un programme de réhabilitation respiratoire : bilan de la première année d'activité. Education thérapeutique du patient – Thepapeutic patient education 9(1):10301

- Médrinal C ; Combret Y ; Prieur G ; Robledo Quesada A ; Bonnevie T ; Gravier FE ; Frenoy E ; Contal O ; Lamia B (2017). Effects of different early rehabilitation techniques on haemodynamic and metabolic parameters in sedated patients: protocol for a randomised, single-bind, cross-over trial. BMJ Open Respir Res 4(1):e000173

- Debeaumont D ; Bota S ; Baste JM ; Bellefleur M ; Stepowski D ; Vincent F ; Bonnevie T ; Gravier FE ; Netchitailo M ; Tardif C ; Boutry A ; Muir JF ; Coquart J (2016). Postpneumonectomy Compression of the Mitral Annulus: Rare Vascular Complication in Sportive Patient. Case Rep Pulmonol 2016(9575894)

- Médrinal C ; Prieur G ; Frenoy E ; Combret Y ; Gravier FE ; Bonnevie T ; Poncet A ; Robledo Quesada A ; Lamia B ; Contal O (2016). Is overlap of respiratory and limb muscle weakness associated with poorer outcome ?. Intensive Car Medicine 43(2):282-3

- Médrinal C ; Prieur G ; Frenoy E ; Robledo Quesada A ; Poncet A ; Bonnevie T ; Gravier FE ; Lamia B ; Contal O (2016). Respiratory weakness after mechanical ventilation is associated with one year mortality – A prospective study. Critical Care 20(1):231

- Bonnevie T ; Villiot-Danger JC ; Gravier FE ; Dupuis J ; Prieur G ; Médrinal, C (2015). Inspiratory muscle training is used in some intensive care units, but many training methods have uncertain efficacy: a survey of French physiotherapists. J Physiother 61(4):204-9

- Gravier FE ; Bonnevie T ; Médrinal C ; Debeaumont D ; Dupuis J ; Viacroze C ; Muir JF ; Tardif C (2015). Noninvasive ventilation during pulmonary rehabilitation in COPD patients. Rev Mal Resp 33(6):422-30

PUBLICATIONS DANS DES REVUES SANS COMITE DE LECTURE

- Bonnevie T ; Prieur G ; Gravier FE ; Combret Y ; Médrinal C (2019). Kinésithérapie et syndrome ventilatoire obstructif, en phase stable. EMC - KINESITHERAPIE-MEDECINE PHYSIQUE-READAPTATION. DOI: 10.1016/S1283-0887(19)56702-0

- Médrinal C ; Prieur G ; Robledo Quesada A ; Gravier FE ; Bonnevie T (2015). La neuro-myopathie de réanimation : physiopathologie et conséquences. Kinésithérapie la Revue 16(169):28-35

- Lesage V ; Gravier FE ; Médrinal C ; Bonnevie T (2015). L'entraînement des muscles inspirateurs : une stratégie efficace dans le sevrage de la ventilation mécanique. Réanimation 25(S2):92-9

- Bonnevie T (2013) Entrainement en force des muscles inspirateurs du patient ventilé – de la dysfonction diaphragmatique au sevrage de la ventilation mécanique. Réanimation 22:439-46

POSTERS/DISCUSSION

- Bonnevie T ; Fresnel E ; Kerfourn A ; Viacroze C ; Muir JF ; Médrinal C ; Cuvelier A ; Gravier FE ; Patout,M (2019). Impact of patient-ventilator asynchronies during exercise with NIV in patients with COPD. 27ème Congrès de l'European Respiratory Society (Poster-Discussion), Madrid, Espagne.

- Bonnevie T ; Gravier FE ; Médrinal C ; Prieur G ; Tardif C ; Muir JF ; Cuvelier A ; Reychler G ; Debeaumont D ; Viacroze C (2018). Nasal vs oronasal interface during exercise under noninvasive ventilation in COPD : a randomized cross-over study. 26ème Congrès de l'European Respiratory Society (Poster-Discussion), Paris, France.

- Bonnevie T ; Gravier FE ; Médrinal C ; Prieur G ; Tardif C ; Muir JF ; Cuvelier A ; Reychler G ; Debeuamont D ; Viacroze C (2018). Nasal vs oronasal interface during exercise under noninvasive ventilation in COPD : a randomized cross-over study. Journée Normand de Recherche Biomédicale, IRIB, Rouen, France.

- Bonnevie T ; Gravier FE ; Médrinal C ; Prieur G ; Viacroze C ; Debeaumont D ; Dupuis J ; Cuveluer A ; Muir JF ; Tardif C (2018). Télémonitoring au cours de la réhabilitation respiratoire : validité d'un système d'oxymérie de pouls à distance. 12ème Journées Francophone Alvéole, Nantes, France.

- Bonnevie T ; Gravier FE ; Leboullenger M ; Médrinal C ; Viacroze C ; Cuvelier A ; Muir JF ; Tardif C ; Debeaumont D (2017) Utilisation du test stepper pour débuter la

réhabilitation respiratoire de patients atteints de BPCO. 21ème CPLF, Marseille, France.

- Debeaumont D ; Bota S ; Baste JM ; Bellefleur M ; Stepowski D ; Vincent F ; Bonnevie T ; Gravier FE ; Netchitailo M ; Boutry A ; Tardif C ; Coquart J ; Compression de l'anneau mitral par l'aorte descendante en post-pneumonectomie chez un patiente sportif. 11ème congrès des Journées Francophones Alvéole, Lyon
- Bonnevie T ; Villiot-Danger JC ; Gravier FE ; Dupuis Johan ; Prieur G ; Villiot-Danger E ; Médrinal C (2015) Implementing Evidence Based Practice in ICU : inspiratory muscle training to wean from mechanical ventilation. Congrès de l'ERS, Amsterdam. European Respiratory Journal 46(suppl59):PA3538

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TRAVAUX DE RECHERCHE EN COURS

- Coordination et obtention de bourses de recherche pour deux travaux portant sur la thérapie à haut débit humidifié :
  - Effets physiologiques aigus de la thérapie à haut débit humidifié à l'effort chez les patients atteints de BPCO sévère à très sévère.
  - Etude contrôlée randomisée évaluant les bénéfices d'un traitement à haut débit humidifié au décours d'un programme de réentraînement à l'effort chez les patients atteints de BPCO sévère à très sévère.
    - **Inclusion en cours**
    - Bourse de recherche ADIR Association : **15 000€**
    - Bourse de vie obtenue auprès Fisher & Paykel, Nouvelle Zélande : **90000€**

- Coordination : Impact sur les performances à l'exercice de différentes interfaces de ventilation non invasive pendant l'effort chez le patient BPCO (ADIR Association)
  - **Collaboration internationale avec Mr Gregory Reychler (Bruxelles, Belgique)**

- Coordination : Utilisation du test stepper pour individualiser le réentrainement à l'effort de patients BPCO léger à modéré (ADIR Association).
  - **Inclusion en cours**
  - **Elargissement de la thématique de recherche pour les patients plus sévères et analyse de la cinétique de VO2 durant le test selon le stade la pathologie**

- Coordination : Télésurveillance de la réhabilitation respiratoire : analyse de la transmission du signal d'un oxymètre de pouls (ADIR Association).
    - **Collaboration internationale avec Mr Mark Elkins (Sidney, Australie)**

- Coordination : Effet de la stimulation nerveuse électrique transcutanée (TENS) lombaire sur la performance à l'exercice de patients atteints de BPCO : une étude pilote.
    - **Développement d'une thématique de recherche en cours**

- Coordination : Effet d'un programme de réhabilitation respiratoire sur les fonctions cognitives de patients atteints de BPCO sévère à très sévère.

New tools and optimization of existing tools for pulmonary rehabilitation and revalidation of patients with ventilatory impairment.

Abstract

Pulmonary rehabilitation (PR) is recommended in the management of subjects with ventilatory impairment to improve their quality of life. Although a large body of evidence support its use, only few subjects benefit from it and the optimal training modality has not been determined yet. In this context, the use of new and existing tools to optimize access as well as the effects of the program are major developments that deserve to be studied.

As part of this thesis, we sought to explore these two major issues (1) by considering a rehabilitation model relocated outside the PR centres while assessing the obstacles to this model and (2) exploring the effectiveness of different add-on to PR in further optimizing the benefits of the program.

In the first part, we have shown, through several retrospective studies and an original prospective multicentre contribution, that the six-minute stepper test can be used to prescribe endurance training, particularly for those patients with a mild to moderate chronic obstructive pulmonary disease (COPD), but not to prescribe muscle strengthening. Furthermore, we have shown in a cohort of 105 subjects referred for PR that the use of a remote tele monitoring device was feasible, valid and widely accepted. Finally, we explored the prevalence of cognitive dysfunction, another systemic impairment of COPD that could compromise the relocation of the program, and showed that it was a very common condition (around 75% of the subjects) but that it could improve following PR and did not seem to influence the use of a remote tele monitoring device.

In the second part, we evaluated the effects of different add-on used to potentiate the benefits of the PR program. In a cross-over study of 21 COPD patients, we showed that non-invasive ventilation did not improve endurance exercise capacity due to technological limitation of the ventilator. Through a multicentre randomized controlled study carried out in 73 patients with severe to very severe COPD, we have shown that neuromuscular electrical stimulation at home, performed in addition to a PR program, did not provide further benefits on quality of life or exercise capacity. Finally, through a randomized cross-over double-blind study carried out in 10 patients, we were unable to show the effectiveness of transcutaneous nerve electrical stimulation in improving their endurance exercise capacity.

Finally, in a last part, we highlighted the research currently carried out in our laboratory following the original contributions described during this thesis, as well as new area of research in order to pursue the themes explored. Thus, two systematic reviews and meta-analysis (the first about nasal high flow therapy in subjects with stable COPD and the second about the use of advanced telehealth technologies to deliver PR) will serve as a basis for future research.

Keywords: Pulmonary rehabilitation; Chronic obstructive pulmonary disease; Cardiopulmonary exercise ; Tele monitoring ; Noninvasive ventilation; Nasal high flow; Electrical stimulation

Nouveaux outils et optimisation des outils existants pour la réhabilitation respiratoire et la ré-autonomisation des patients atteints de handicap ventilatoire.

Résumé

La réhabilitation respiratoire (RR) est recommandée dans la prise en soin des patients atteints d'un handicap ventilatoire afin d'améliorer leur qualité de vie. Malgré une efficacité clairement établie, très peu de patients en bénéficient et les modalités optimales d'entrainement restent à définir. L'utilisation des outils existants et des nouveaux outils pour optimiser l'accès au programme et ses effets représentent des développements majeurs qui méritent d'être évalués.

Dans le cadre de cette thèse, nous avons cherché à aborder ces deux problématiques (1) en tentant de proposer un modèle de RR délocalisée hors des centres tout en évaluant les freins à ce modèle et (2) en explorant la place de différents adjuvants à la RR afin d'en optimiser les bénéfices.

Dans la première partie, nous avons montré, à travers plusieurs études rétrospectives et une contribution originale prospective multicentrique, que le test stepper de six minutes peut être utilisé pour prescrire l'entrainement en endurance, particulièrement pour les patients présentant une forme légère à modérée de bronchopneumopathie chronique obstructive (BPCO), mais pas pour prescrire le renforcement musculaire. Par ailleurs, nous avons montré dans une population de 105 patients adressés en RR que l'utilisation d'un dispositif de telemonitoring était faisable, valide et largement accepté. Enfin, nous avons exploré la prévalence des dysfonctions cognitives, autre conséquence systémique de la BPCO qui pourrait compromettre la délocalisation du programme, et avons montré que cette prévalence était très élevée (environ 75% des patients) mais que ces troubles cognitifs pouvaient s'améliorer après la RR et ne semblaient pas influencer l'utilisation d'un dispositif de telemonitoring.

Dans la seconde partie, nous avons évalué la place de différents adjuvants à la RR utilisés pour en potentialiser les bénéfices. Dans une étude en cross-over menée chez 21 patients atteints de BPCO, nous avons montré que la ventilation non invasive ne permettait pas d'améliorer la capacité à l'exercice en endurance en raison d'une limitation technologique du ventilateur. A travers une étude contrôlée randomisée multicentrique menée chez 73 patients atteints de BPCO sévère à très sévère, nous avons montré que la stimulation électrique excito-motrice à domicile, réalisée en plus d'un programme de RR, n'apportait pas davantage de bénéfices sur la qualité de vie ou la capacité à l'exercice. Enfin, à travers une étude randomisée en cross-over et en double aveugle menée chez 10 patients, nous n'avons pas pu montrer l'intérêt de la stimulation électrique nerveuse transcutanée pour améliorer leur capacité à l'exercice en endurance.

Enfin, dans la dernière partie, nous avons présenté les recherches actuellement menées au sein de notre laboratoire, faisant suite aux contributions originales décrites au cours de cette thèse, ainsi que de nouvelles pistes de recherche afin de poursuivre les thématiques explorées. Ainsi, deux revues de littérature et méta-analyses (l'une d'elle portant sur le haut débit nasal et l'autre sur l'utilisation des technologies de santé avancées pour réaliser la RR respiratoire à domicile) serviront de base pour de futurs travaux.

Mots Clés : Bronchopneumopathie chronique obstructive ; Réhabilitation respiratoire ; Evaluation ; Telemonitoring ; Ventilation non-invasive ; Thérapie à haut débit humidifié ; Electrostimulation.