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Original Article

Nasal high-flow therapy as an adjunct to exercise in patients with cystic fibrosis: A pilot feasibility trial☆

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ABSTRACT

Background: Exercise tolerance in people with CF and advanced lung disease is often reduced. While supplemental oxygen can improve oxygenation, it does not affect dyspnoea, fatigue or comfort. Nasal high-flow therapy (NHFT), thanks to its pathophysiological mechanisms, could improve exercise tolerance, saturation and dyspnoea. This study explores the feasibility of conducting a clinical trial of using NHFT in patients with CF during exercise.

Methods: A pilot, open-label, randomized crossover trial was performed, enroling 23 participants with CF and severe lung disease. Participants completed two treadmill walking test (TWT) with and without NHFT at 24–48 h interval. Primary outcome was trial feasibility, and exploratory outcomes were TWT distance (TWTD), SpO_2, transcutaneous CO_2, dyspnoea and comfort.

Results: Recruitment rate was 2.4 subjects/month with 1.3:1 screening-to-randomization ratio. No adverse events caused by NHFT were observed. Tolerability was good and data completion rate was 100%. Twenty subjects (91%) were included in the exploratory study. Mean difference in TWTD on NHFT was 19 m (95% CI [4.8 - 33.1]). S_pO_2 was similar, but respiratory rate and mean $tcCO_2$ were lower on NHFT (mean difference = -3.9 breaths/min 95% CI [-5.9 - -1.9] and -0.22 kPa 95% CI [-0.4 – 0.04]). NHFT reduced exercise-induced dyspnoea and discomfort.

Conclusion: Trials using NHFT in patients with CF during exercise are feasible. NHFT appears to improve walking distance, control respiratory rate, CO_2, dyspnoea and improve comfort. A larger trial with a longer intervention is feasible and warranted to confirm the impact of NHFT in training programmes for patients with CF.

Introduction

Cystic fibrosis (CF) is a progressive, multi-system disease that primarily affects the respiratory system [1]. Despite significant improvement in the care of patients with CF and in life expectancy, approximately 20% of patients continue to develop severe lung disease by the age of 30 [2].

Aerobic exercise remains an integral part of the management of people with CF, and is associated with a reduction of the rate of decline in lung function and improved quality of life and bone mineralisation [3–7]. However, disease progression and the associated structural damage results in increased airway resistance, static and dynamic hyperinflation, hypoventilation and ventilation-perfusion mismatch, all of which reduce exercise tolerance [8–11]. Patients can present with dyspnoea and fatigue during exercise, with exercise-induced hypoxaemia or desaturation occurring in 15 to 30% of cases [12,13]. Short-term oxygen can improve oxygen saturation (SpO_2) during or immediately after an exercise bout, with

Abbreviations: 6MWD, 6-minute walking distance; Borg-d, dyspnoea score according to borg scale; Borg-f, fatigue score according to borg scale; Cf, cystic fibrosis; Fev, forced expiratory volume in 1 second; FVC, Forced vital capacity; NHFT, Nasal high-flow therapy; RR, Respiratory rate; TWT, treadmill walking test.

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an increase in end tidal carbon dioxide (CO_2) compared to room air, but does not affect exercise tolerance, dyspnoea or fatigue [14].

Nasal high-flow therapy (NHFT) delivers heated, humidified, and oxygenated gas with flowrates up to 60 L/min at varying fraction of inspired oxygen (F_IO_2) between 0.21 and 1.0 via soft, loose fitting, large bore nasal prongs. NHFT has been shown to wash out nasopharyngeal dead space, thereby minimizing CO_2 rebreathing and providing a reservoir for fresh air. In addition, NHFT has been shown to reduce respiratory rate and increase tidal volume and, by delivering high flow of humidified gas, it more closely matches the patient's inspiratory flow rate and reduces airway dryness [15]. By virtue of all these pathophysiological mechanisms, NHFT has been proved as an effective alternative method to NIV or conventional oxygen therapy in a variety of clinical scenarios. Recently, NHFT was shown to increase exercise tolerance in patients with COPD, showing improved oxygen saturation and dyspnoea [16,17]. Evidence on the use of NHFT in CF is available but limited.

The aim of this study was to assess the feasibility of conducting a trial using NHFT during exercise in patients with CF and advanced lung disease, and to preliminarily explore its clinical effect during a treadmill 6-minute walking test (TWT).

Methods

Study design and participants

An open, single-centre, short-term, pilot feasibility trial with a randomized cross-over design comparing NHFT to baseline conditions during a TWT was performed in the Leeds Regional Adult CF Centre (Leeds, UK). The study was approved by HRA (19/LO/0571) and local R&I (RM19/121,917), was conducted in accordance with the Declaration of Helsinki and was registered on clinicaltrials.gov (NCT03965832). Written informed consent was obtained from all participants.

Eligible participants included patients admitted to the Leeds CF Unit, aged $\geq$18 years, with a confirmed diagnosis of CF and known advanced lung disease (defined as FEV_1 <40% in the 6 months prior the admission). Exclusion criteria included: acute viral illness with positive viral PCR on nose and throat swab in the 5 preceding days, need for 6 L/min or more of oxygen at rest, decompensated type-2 respiratory failure, pneumothorax in the 6 preceding weeks, usual contraindications to a 6 min walking test [18] and inability to provide consent.

Consecutive patients admitted to the Unit who met the inclusion and exclusion criteria were approached to assess eligibility in study participation during hospital admission for pulmonary exacerbation, and if agreed to take part, were recruited during second week of treatment once deemed clinically stable by the clinical team.

Study outcomes

The aim of this study was assessing the feasibility of performing larger trials of NHFT in individuals with CF as an adjunct during exercise.

Primary outcome was recruitment rate, and secondary outcomes were screening-to-randomization rate, dropout rate, data completion rate, participants' willingness to participate in future trials and side effects.

Clinical outcomes of interest were established to explore clinical effects and to power future trials. The primary exploratory outcome of interest was 6-minute walking distance (6MWD). Other outcomes of interests were mean and nadir oxygen saturation during exercise, mean transcutaneous carbon dioxide ($tcCO_2$), SpO_2 recovery time, change in RR, dyspnoea, fatigue and comfort during the TWT.

Study procedures

Upon enrolment, all subjects underwent a baseline arterialised capillary blood gas (CBG).

Subjects performed two TWTs, with NHFT (NHFT-test) and without (control-test). To minimize bias due to the unblinded design and reduce the potential effects related to the recovery from a pulmonary exacerbation, the two TWTs were performed in a random order at interval time of 24–48 h. Randomization was done in a masked fashion and performed in permuted blocks of 10 with a computer generated random-number sequence, with a 1:1 allocation.

Subjects were familiarized on how to use the treadmill and instructed prior to beginning study procedures. No warm-up period before the test was performed, but subjects were asked to rest sitting in a chair for 30 min (acclimation period).

During the treadmill walking test, participants were directed as per ATS guidelines [18]. Initial speed was set at 2.5 km/h, and subjects were able to adjust the speed as they wished. The control test was performed on room air or conventional supplemental oxygen, delivered via nasal cannulae or Venturi mask, according to each subject's habitual prescription. NHFT was delivered through nasal cannulae (Optiflow+, Fisher&Paykel Healthcare NZ) using the Airvo 2 (Fisher&Paykel Healthcare, NZ), with size chosen based on manufacturer recommendations.

On the day of the NHFT-test, as part of the acclimation period, subjects were first started on NHFT for 15 min at 30 L/min, 37 C, and subsequently increased at 45 L/min for 15 more minutes. During the TWT, flow-rate was maintained at 45 L/min and F_IO_2 was set to match what usually prescribed during exercise for each subject. During the resting period, subjects were asked to continue using the NHFT for 30 min.

The distance walked (WD) on the treadmill was recorded, as well as the highest and lowest speed reached. Throughout the study, subjects were continuously monitored for oxygen saturation and transcutaneous carbon dioxide using a Sentec Digital Monitor V-sign sensor (Sentec AG, Switzerland). Furthermore, blood pressure (BP), respiratory rate (RR), Borg scale for dyspnoea (Borg-D), and leg fatigue (Borg-F) and comfort score were recorded every 15 min during the acclimation period, and every two minutes both during the TWT and in the 10 min after its end.

Spirometry was performed according to the ERS guidelines, 30 min before and after the TWT, to allow for a rest period, using an Alpha Touch Spirometer (Vitalograph, UK).

Fig. 1 schematises the study procedures.

Data collection

Baseline demographic data, comorbidities, use of supplemental oxygen or non-invasive ventilation, and status on the lung transplant waiting list were collected from medical notes. Lung function on admission and baseline blood gas results were also recorded.

Patient and public involvement

The study design and protocol were discussed in a face-to-face meeting with a patient representative of the group included in the study. The research questions were deemed of interest for individuals with CF and the methods used during the study were considered not too intrusive or burdensome.

Statistical analysis

No formal sample size calculation was performed. Based on expected capability of recruitment within the unit and previous studies on respiratory support during exercise [19] and on NHFT in CF

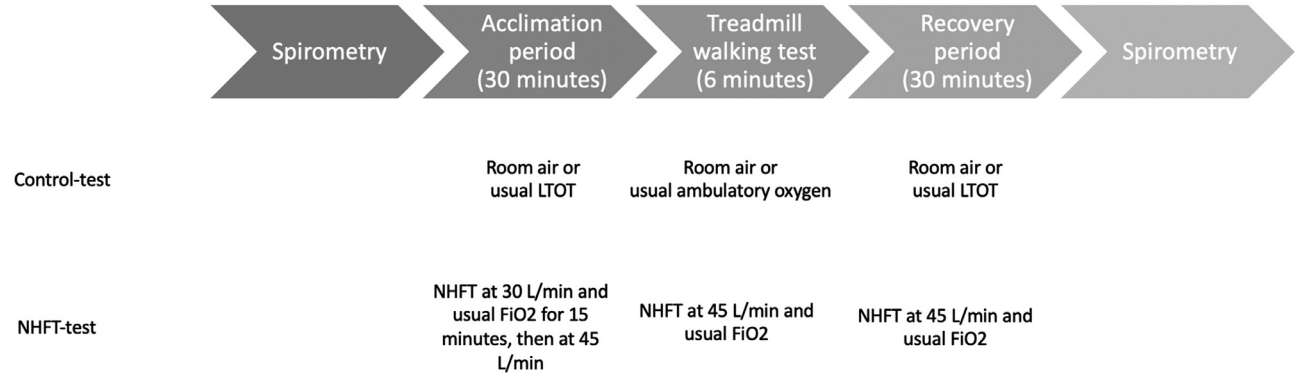

Fig. 1. Schematics of the methodology during each session of the trial. The order the two conditions were delivered was randomized. Interval time between tests was 24–48 h.

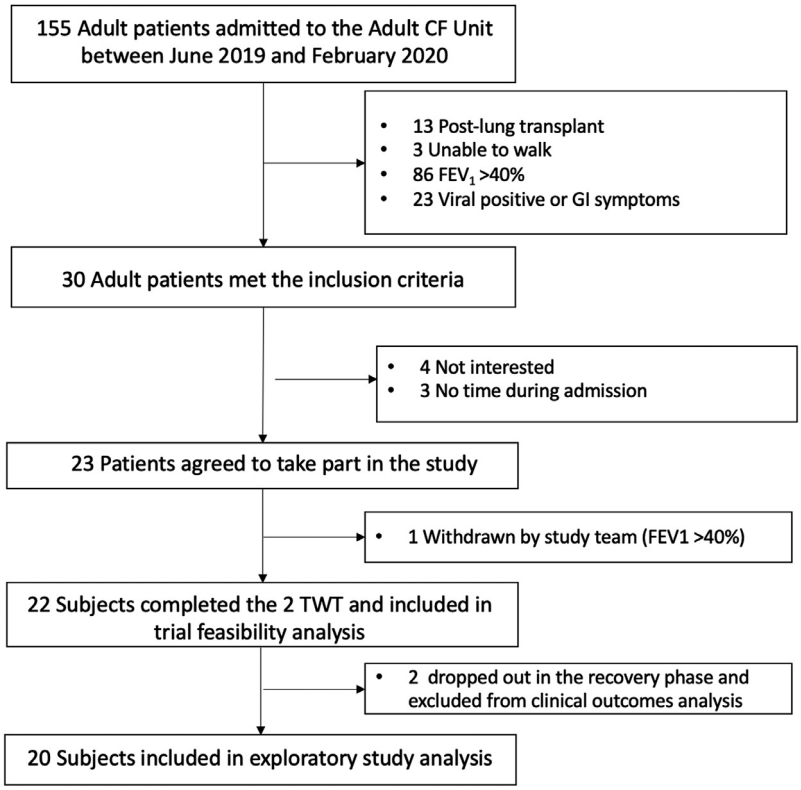

Fig. 2. Flow-chart of patient recruitment and inclusion in the study and analysis.

[20], we planned to enrol up to 25 subjects, in order to achieve a full data set on 20 subjects, expecting a drop-out rate of up to 20%.

Normal distribution of each measured variable was assessed by visual inspection and using the Shapiro-Wilks test. Results are expressed as number (percentage), means (standard deviation) when normally distributed, or median (25th-75th percentile) when not normally distributed. Paired *t*-test for parametrical data or Wilcoxon test for non-parametric data was used to compare each variable in the two walking tests (NHFT- and control-test). Estimates of effect size are provided with 95% confidence interval (95% CI). A p-value < 0.05 was considered statistically significant. All analyses were performed with IBM SPSS v26.

Results

Subjects

Between June 2019 and February 2020, 155 patients were admitted to the Cystic Fibrosis Unit at Leeds Teaching Hospital, thirty of whom met the inclusion criteria for the study and were screened for participation. Twenty-three patients consented to take part in the study, one was withdrawn by the study team as FEV_1 had transiently increased >40% (Fig. 2). Despite the initial plan to enrol up to 25 subjects, in view of the COVID-19 pandemic, enrolment was closed after enroling 23 patients.

The study population was female predominant ($n = 12$, 54.5%), with a median age at 34 years. Most participants ($n = 15$, 68.2%) were on CFTR modulator therapy and were under consideration for lung transplantation ($n = 8$, 36.4%) or on the active waiting list for lung transplant ($n = 7$, 31.8%) (Table 1).

Trial feasibility

The recruitment rate was on average 2.4 subjects per month, with screening to randomization ratio of 1.3:1 (76.7%). One subject was withdrawn as no longer meeting the inclusion criteria on day 1 of the study (baseline lung function transiently increased above 40%). Two subjects completed the walking tests on both conditions

Table 1
Baseline characteristics of study population.

	n = 22
Age	34 [29.5–39]
Male sex, n (%)	10 (45.5%)
BMI	20.9 [18.6 –22.1]
Genotype	
F508del/F508del	12 (54.5%)
F508del/-	9 (41%)
Other	1 (4.5%)
CFTR modulator	
Ivacaftor	3 (13.6%)
Double therapy (LUM/IVA or TEZ/IVA)	11 (50%)
Triple therapy (ELX/TEZ/IVA)	1 (4.5%)
None	7 (31.8%)
Transplant	
Not yet considered	7 (31.8%)
Under consideration	8 (36.4%)
Declined	4 (18.2%)
Active list	3 (13.6%)
Comorbidities	
Diabetes	4 (18.2%)
Liver disease	9 (41%)
Low bone mineral density	14 (63.6%)
Arthritis	4 (18.2%)
Microbiology	
Chronic P.aeruginosa	16 (72.7%)
MRSA	2 (9.1%)
M. abscessus	4 (18.2%)
BCC	2 (9.1%)
Respiratory support	
LTOT	5 (22.7%)
Nocturnal Oxygen	3 (13.6%)
Ambulatory oxygen	3 (13.6%)
NIV	5 (22.7%)
FEV1 on admission, L	0.83 [0.65–1.06]
FEV1 on admission,%	25 [16-31]
CBG at baseline	
pH	7.43 [7.41–7.46]
pCO_2	5.48 [4.8 – 6.03]
pO_2	9.2 [8.6 – 9.7]
HCO_3^-	27 [23.7 – 28.5]

but dropped out before the recovery phase of the NHFT-test as they did not tolerate the device. Data completion rate was 100% for the twenty subjects who completed the study.

Tolerability was good. All but two subjects expressed a positive experience about participating in this research study and indicated that they would take part in longer term studies on the use of HFNT during exercise. The two subjects who reported negative experience required reduction in the temperature during NHFT-test and asked to stop using the device after completion of data collection of the walking test 15 min in the resting period.

One subject, who did not tolerate the device, reported chest pain during the TWT on NHFT. This was not associated with any change in vital signs and, on history review, was not deemed to be caused by NHFT.

Lung function was not adversely affected when using NHFT, with no episode of bronchoconstriction secondary to the use of NHFT.

Exploratory clinical outcomes of interest

By virtue of the exploratory aims of this study, clinical outcomes of interests were assessed on the 91% of subjects (n = 20 out of 22) who tolerated the device and completed the study in full. Table 2 summarises the results of the exploratory outcomes of interest.

All subjects completed both the NHFT- and control-tests with no interruptions. WD was significantly higher on NHFT than on baseline conditions (mean difference = 19 m [95% CI 4.8 - 33.1], p = 0.01). No differences in highest or lowest speed recorded during the test were observed.

Table 2
Exploratory clinical outcomes of interest of the pilot trial.

	Control test (n = 20)	NHFT-test (n = 20)	p
Walking distance, m	430 [352–537]	450 [360–550]	0.013
Recovery time, sec	51.5 [0–114]	54.5 [10-75]	0.7
SpO2,%			
Mean	93 [91–95]	92.75 [90–95]	0.138
Nadir	89 [86–92.75]	88 [83–93]	0.255
Mean tcCO2, kPa	5.35 [4.99–5.44]	4.89 [4.56–5.47]	0.03
Respiratory rate			
At start	22 [20-24]	16 [13-18]	<0.001
At end	30 [26-34]	26 [20-30]	0.003
Borg – dyspnea			
At start	0 [0–0.875]	0.25 [0–1.75]	0.07
At 2 min	2 [0.5–2.875]	1.5 [1–2.875]	0.88
At 4 min	3 [1–3.875]	3 [1.25–3]	0.38
At end	3 [1.275–4.75]	3 [1.25–4]	0.33
Borg – Fatigue			
At start	0 [0–0]	0 [0–1]	0.246
At 2 min	0.75 [0–2]	1 [0.5–2]	0.916
At 4 min	1.5 [0–2.375]	1.25 [0.125–2.375]	0.759
At end	2 [0.125–3.625]	2 [0.5–4]	0.905
Comfort score			
At start	10 [9-10]	8 [6.125–10]	0.003
At 2 min	9 [8–9.75]	8 [7–8.75]	0.03
At 4 min	8 [6-9]	7.75 [6.25–8]	0.426
At end	8 [5-9]	7 [5.25–8]	0.566

tcCO2 – transcutaneous carbon dioxide level, SpO2 – oxygen saturation.

Mean and nadir S_pO_2, as well as recovery time for S_pO_2 were similar for the control and NHFT conditions both before and during the TWT (Table 2).

Respiratory rate at the end of the TWT was significantly lower on NHFT than during the control test (mean difference = −3.9 breaths/min [95% CI −5.9 - −1.9], p = 0.001). Mean transcutaneous CO_2 was also lower on NHFT compared to the control test (mean difference = −0.22 kPa [95% CI −0.4 – 0.04], p = 0.019).

Comfort score was better at the start of the test on control condition, but Borg-D was similar. When comparing the same scores at the end of each TWT, no differences were observed in comfort, Borg-D and Borg-F across the whole dataset (Table 2).

Fig. 3 shows the relative change in comfort and dyspnoea during the TWT. A lesser reduction in comfort was observed during NHFT-test compared to control test (mean difference in delta comfort = 1.3 [95% CI 0.2 – 2.5], p = 0.024).

The increase in Borg-D during the TWT was lower during the NHFT-test compared to the control-test (mean difference in delta Borg-D = −0.57 [95% CI −1.13 – −0.2], p = 0.044).

Discussion

To the best of our knowledge, this is the first study exploring the use of NHFT as an adjunct during exercise in individuals with cystic fibrosis.

In this pilot study, we showed that it would be feasible to conduct trials using NHFT during aerobic exercise in adults with CF. Exploratory outcomes of interests for efficacy indicated that NHFT might improve 6MWD amongst individuals with CF and advanced lung disease, and reduce respiratory rate and carbon dioxide during exercise. Dyspnoea, comfort and oxygen saturation were stable throughout exercise on NHFT.

Recruitment target was achieved within 9 months from starting the study, 10 months ahead of scheduled time. Screening failure rate was low, and screening to randomization rate was good, suggesting suitability of the recruitment strategies and eligibility criteria. Two subjects dropped out during the recovery phase of the

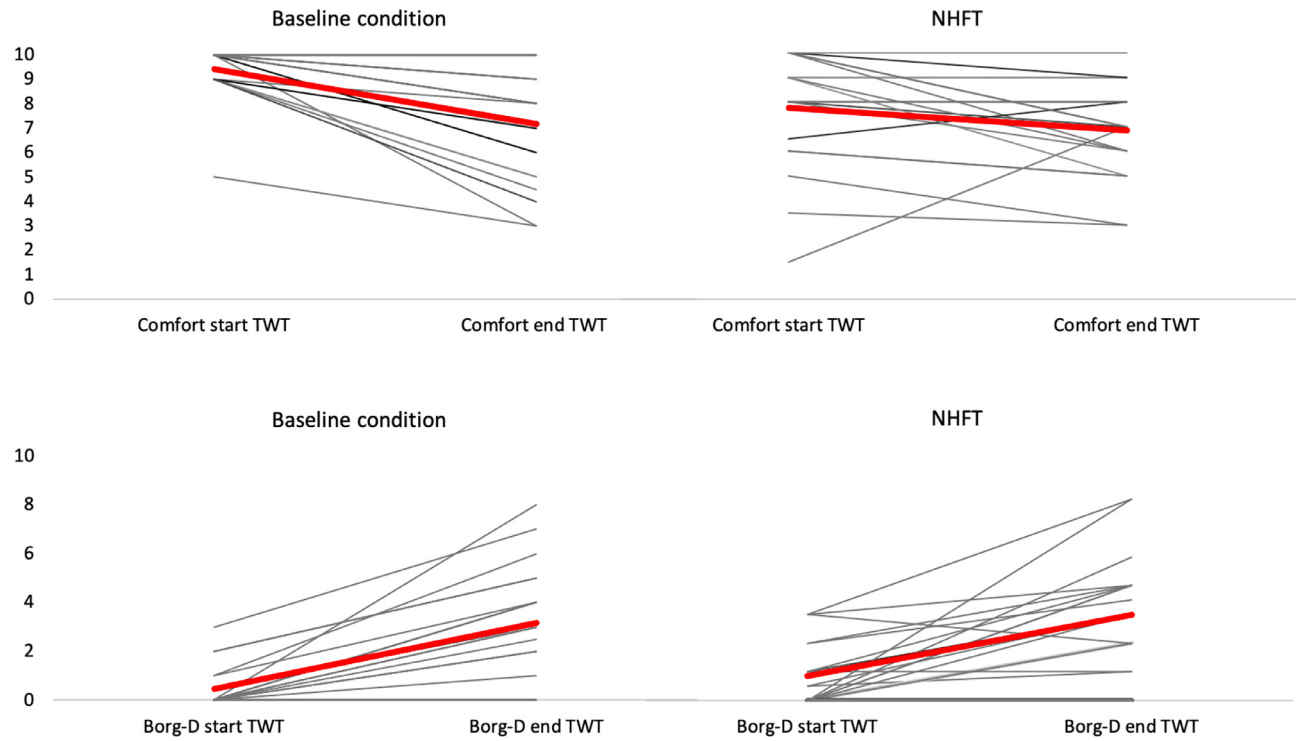

Fig. 3. Change in comfort and dyspnoea score during the TWT on baseline conditions and on NHFT. Individual data are presented in grey lines, mean data are presented in red lines.

NHFT-test, providing a 9% of drop-out rate, much lower than the planned 20%.

Participants provided positive feedback on this study and showed interest in participating to longer trials. This highlighted that the study procedures were deemed acceptable, and that future trials exploring the role of NHFT during longer training programmes would be feasible in terms of recruitment. Training programmes in CF would have to be performed remotely with participants exercising in their home environment to reduce their risk of cross-infection.

In our cohort, two patients (9%) did not tolerate the device and reported unwillingness to repeat similar trials. On visual inspection of their characteristics, these patients had marked reduction of the FVC (< 1 L) and were significantly underweight. As FVC correlates with peak inspiratory flow, it is conceivable that the flow-rates delivered by NHFT are disproportionate for patients with significant reduction in FVC.

In planning future trials, we would therefore suggest that inclusion criteria should be adapted in light of this finding. In particular, we would consider a dropout rate of at least 10% to account for participants who might not tolerate the device, decide to stop participation due to the longer nature of a study in the home environment and/or experience clinical deterioration. In addition, we would suggest amending inclusion criteria to either exclude subjects with FVC < 1 L who, in our pilot study, reported significant discomfort and disliked the device, or planning a prespecified stratification based on FVC to further explore tolerability in the subgroup with significant reduction in FVC.

This pilot study was not designed to assess intervention efficacy, however, exploratory outcomes showed improvement in distance walked during the TWT. While CPET is the gold standard to assess globally the response to exercise [21], its use in CF is limited and most patients are routinely assessed with 6-minute walking test, which has been shown to have good correlation with the peak oxygen uptake in patients with severe lung disease, to be reliable and repeatable [22–24]. In this study, a treadmill walking test was preferred to a standard 6MWT, as commonly done in previous trials in this population [19,25], in view of infection control policies to reduce the risks of cross-infection.

Currently, no threshold for minimally clinically important difference (MCID) for change in treadmill or over-grounds 6-minute walking distance is defined for people with CF [18]. Previous studies on patients with COPD and pulmonary hypertension showed a variable correlation between the TWD and 6MWD, but consistently more favourable results when the walking test was performed on grounds rather than on the treadmill [26–28]. A recent systematic review proposed that any change in 6MWD on grounds between 14 and 30.5 m should be considered a MCID across multiple patients' group [29]. In our study, patients underwent TWT rather than conventional 6-minute walking test. This notwithstanding, the improvement in WD observed in our study is statistically significant and within this proposed range (19 m mean difference) and well above the mean difference observed for repeated test (8 m) in people with CF [24].

The intra-test comparison showed that respiratory rate before and after the TWT increased at similar magnitude during both the NHFT and the control tests. However, respiratory rate was lower on NHFT compared to baseline conditions across the whole study, starting from acclimation period to the end of the walking test. The change in RR was of the same magnitude of what observed in a recent crossover trial comparing NHFT to NIV and baseline conditions in stabilised patients with CF admitted with pulmonary exacerbation [20]. This, in association with the observed reduction in carbon dioxide level, suggest the NHFT could contribute to a change in breathing pattern and minute ventilation as previously observed during exercise on NHFT in people with severe COPD, and in patients with CF recovering from exacerbations [16,20].

NHFT has been reported to improve comfort in various scenarios compared to both baseline conditions and NIV [15,30,31]. In keeping with what reported in [20], our study shows that peo-

ple with CF reported lower comfort when started on NHFT at rest. However, comfort at end of exercise was comparable in the two conditions, and decreased more during the control test. Similarly, dyspnoea measured with the Borg scale was similar at the start of the test in both conditions but increased to a lesser extent during the NHFT test. These findings suggest that relatively stable patients might not benefit from NHFT deliver at flowrates at 30 L/min or higher, as they are not in any respiratory distress. However, once their respiratory demands increased during exercise, the additional support provided by NHFT might be beneficial.

The main limitation of this study, similarly to any trial using NHFT, is the lack of blinding, as no sham device is available for the control-test. However, none of the participants had used NHFT ahead of their participation in the trial. In addition, we could not adequately measure minute ventilation during exercise due to the inability to use a pneumotachograph on NHFT, and inductive plethysmography would lead to artefacts by movement. However, while the absence of measurements of breathing pattern can limit the interpretation of some of the exploratory outcomes (such as respiratory rate, and carbon dioxide), it does not affect the effect observed for this treatment.

Finally, while the exploratory outcome of interest provided positive results, the study was not powered for efficacy outcomes given the pilot nature and changes in WD are best observed after a training programme. As such, these findings need to be confirmed and further investigated in adequately powered trials to assess the longer-term effects of NHFT during exercise training programme in people with CF.

Conclusion

This pilot study showed that it would be feasible to recruit for trials assessing the potential role of NHFT during exercise in CF. Our exploratory results suggest that using NHFT during exercise in people with CF and advanced lung disease appears to be beneficial in increasing walking distance, reducing their respiratory rate and carbon dioxide, and achieving a better control of dyspnoea and comfort compared to baseline conditions.

Further studies to explore the use of NHFT during a longer-term physical training programme in people with cystic fibrosis and severe lung disease are warranted by the results of this pilot.

Credit Author Statement

Giulia Spoletini: protocol design, data collection and analysis, manuscript writing and revision. Dr Spoletini is the guarantor of the content of the manuscript, including the data and analysis.

Ruth Watson: data collection, manuscript revision.

Wang Yng Lim: data collection, manuscript revision.

Kim Pollard: data collection, manuscript revision.

Christine Etherington: data collection, manuscript revision.

Ian Clifton: data collection, manuscript revision.

Daniel Peckham: protocol design, manuscript revision.

Declaration of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Conferences

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