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Effect of portable non-invasive ventilation on exercise tolerance in COPD: one size does not fit all

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Abstract

In a cross-over RCT, portable NIV (pNIV) reduced dynamic hyperinflation (DH) compared to pursed lip breathing (PLB) during recovery from intermittent exercise in COPD, but not consistently in all subjects. In this post-hoc analysis, DH response was defined as a reduction ≥4.5% of predicted resting inspiratory capacity with pNIV compared to PLB.

At exercise iso-time (where work completed was consistent between pNIV and PLB), 8/24 patients were DH non-responders (DH: 240±40ml, p=0.001 greater using pNIV). 16/24 were DH responders (DH: 220±50ml, p=0.001 lower using pNIV). Compared to DH responders, DH non-responders exhibited greater resting DH (RV/TLC: 65±4% versus 56±2%; p=0.028) and did not improve exercise tolerance (pNIV: 30.9±3.4 versus PLB: 29.9±3.3 min; p=0.603). DH responders increased exercise tolerance (pNIV: 34.9±2.4 versus PLB: 27.1±2.3 min; p=0.001). Resting RV/TLC% was negatively associated with the magnitude of DH when using pNIV compared to PLB (r=-0.42; p=0.043).

Patients with profound DH were less likely to improve exercise tolerance with pNIV. Further studies using auto-adjusted ventilators are warranted.

Highlights

- The study provides proof of concept on how to select COPD patients likely to respond to portable NIV (pNIV) during intermittent exercise.
- One third of patients (8/24) did not improve dynamic hyperinflation (DH non-responders) with the application of pNIV compared to pursed lip breathing (PLB).
- DH non-responders exhibited greater resting hyperinflation and tend towards worse spirometric measures compared to responders.
- Exercise endurance was improved by using pNIV compared PLB in DH responders, but unchanged in non-responders.
- Further studies in auto-adjusted ventilators are warranted in patients with severe COPD.

1. Introduction

In patients with COPD dynamic hyperinflation (DH) is associated with breathlessness and reduced exercise endurance. This affects functional independence, the ability to carry out activities of daily living, and quality of life (QOL) [Spruit, et al. 2013]. Pulmonary rehabilitation (PR) is a cornerstone of COPD treatment and improves exercise tolerance and QoL [Spruit, et al. 2013]. However, in patients with moderately severe and severe COPD presenting with exertional breathlessness, it is difficult to achieve the necessary intensity of exercise during PR to induce true physiological training effects [Maltais, et al. 1997].

A variety of exercise training and ergogenic strategies aimed at reducing breathlessness have been described and evaluated within the literature, including intermittent exercise [Vogiatzis, et al. 2002], oxygen [O'Donnell, et al. 2001a] and heliox supplementation [Palange 2010] and Non-Invasive Ventilation (NIV) [Ambrosino and Cigni 2015,Ambrosino and Xie 2017]. Use of NIV has shown clinically meaningful benefits to exercise tolerance, DH and breathlessness, however there are limitations with the practical application of this approach during exercise in patients with COPD [Ambrosino and Cigni 2015,Ambrosino and Xie 2017]. Accordingly, investigating more effective ways to administer NIV in rehabilitation or exercise programs is justified [Vogiatzis, et al. 2019].

A novel hand-held, battery powered, portable NIV (pNIV) device (VitaBreath, Philips Respironics), provides bi-level positive airway pressure (BiPAP) and can be easily applied during recovery from exercise [Hardy and Jasko 2015]. Conventional NIV is used during exercise in COPD. However, according to the manufacturers' specifications this particular hand held device was made to be used during daily

living activities in COPD to assist recovery of activity-related breathlessness [Hardy and Jasko 2015] thus, cannot be used during exercise. The VitaBreath device is no longer commercially available, but similar devices may come to market; the present study provides proof of concept on how pNIV can be applied intermittently during exercise in patients with COPD, and how to select patients most likely to respond. This in turn may also encourage development of more suitable devices.

Our previous randomised crossover study showed that in COPD use of pNIV during recovery periods within intermittent exercise prolonged exercise endurance and reduced DH and breathlessness compared to pursed lip breathing (PLB) [Vogiatzis, et al. 2019]. However, pNIV did not improve outcomes in all subjects; 8/24 patients failed to show a clinically significant improvement in DH (≥4.5% of predicted resting inspiratory capacity) using pNIV compared to PLB and were defined as 'DH non-responders' [Vogiatzis, et al. 2019]. One technical limitation of this pNIV device is that the expiratory and inspiratory positive airway pressures (EPAP=8cmH_2O and IPAP=18 cmH_2O, respectively) are fixed, and therefore may have been sub-optimal in at least some of the patients.

The aim of the present study was to compare the baseline characteristics, the respiratory and circulatory response during exercise and qualitative outcomes between DH responders and DH non-responders. We defined response in terms of DH as it is an objective physiological index that determines the clinical response. Whilst the primary outcome in the original RCT was exercise endurance, this is influenced by a variety of factors, some of which are subjective. Exercise endurance was included as an outcome measure.

2. Methods

2.1 Study design

This is a retrospective analysis conducted on data collected during a prior randomised open-label crossover trial comparing the use of pNIV to PLB during two exercise protocols; namely a high-intensity or a moderate-intensity intermittent exercise protocol [Vogiatzis, et al. 2019]. In accordance with the official ERS statement on the use of exercise testing in the evaluation of interventional efficacy [Puente-Maestu, et al. 2016] physiological variables recorded when using pNIV or the PLB were compared at exercise iso-time (where work complete was consistent between application of pNIV and PLB), therefore allowing comparisons to be made which were unaffected by the use of the different intermittent exercise protocols applied in the previous study [Vogiatzis, et al. 2019]. All investigations were carried out following ethical approval from the NHS Research Ethics Committee (REC: 17/NE/0085) and following protocol submission for Clinical Trials Registration (NCT03068026). All studies were carried out in line with the Declaration of Helsinki. All participants provided written informed consent.

2.2 Participants

In the present analysis we included data from all 24 stable COPD patients who were included in the original study; inclusion and exclusion criteria have been described elsewhere [Vogiatzis, et al. 2019].

2.3 Baseline Assessment

Prior to exercise testing, participants attended North Tyneside General Hospital for baseline assessment including spirometry, body plethysmography lung volume measurements, diffusion capacity and resting ECG evaluation [Vogiatzis, et al. 2019]. Following medical assessment, patients performed a ramp incremental cardiopulmonary exercise test to the limit of tolerance to establish presence of DH [Vogiatzis, et al. 2019,O'Donnell, et al. 2001b] and define peak work rate (WRpeak). All participants attended 6-8 practice exercise sessions with a qualified physiotherapist, where they were instructed of the correct PLB technique and use of the pNIV device prior their participation to the study [Vogiatzis, et al. 2019].

2.4 Intermittent Exercise Protocols

Participants were randomised to a high-intensity (HI; n=13) or a moderate-intensity (MOD, n=11) intermittent exercise protocol to the limit of tolerance using the pNIV or the PLB method in a balanced ordering sequence. HI consisted of 2-min cycling at 80% WRpeak alternated with 2-min recovery periods (Figure 1a). MOD consisted of 6-min cycling at 60% of WRpeak alternated with 2-min recovery periods (Figure 1b). In the first minute of each recovery period (either HI or MOD), participants were instructed to use either the pNIV device or the PLB technique in the predetermined balanced order. At rest and during the second minute of recovery patients were instructed to perform inspiratory capacity (IC) manoeuvres to assess DH [O'Donnell, et al. 2001b]. Pulmonary gas exchange, ventilatory variables and IC measurements were performed using a portable gas exchange analyser (K4b^2, Cosmed, Shepperton, UK) at rest and throughout exercise testing. A portable cardio-impedance device

(Enduro, Physio flow, Manatec) was used to assess cardiac output throughout exercise testing. At predefined time points during exercise and at the limit of tolerance, patients were instructed to perform IC manoeuvres (Figure 1c). The Modified Borg Scale was used to assess the magnitude of dyspnoea and leg discomfort during the second minute of each recovery period [Borg 1982]. The exercise procedures and assessments have been explained in detail elsewhere [Vogiatzis, et al. 2019].

2.5 Use of pNIV in daily life

Following completion of the exercise tests, all patients were provided with the VitaBreath device to use during daily life activities as they wished. Use of, and perceived benefit from, the VitaBreath device was assessed at 2 and 12 weeks post exercise testing. The survey included questions on symptom burden, ability to perform daily tasks and perceived benefit from the device. The components of the survey can be found elsewhere [Vogiatzis, et al. 2019].

2.6 Statistical analysis

Data are presented as mean±SEM rather than SD because the comparisons of interest were in the mean values of various physiological variables under the two different breathing modalities (pNIV and PLB). As exercise time was different between the pNIV and PLB trials within the HI and MOD intermittent protocols, physiological measures were compared at the time point where the shortest trial (pNIV or PLB) was terminated (i.e., at exercise iso-time) [Puente-Maestu, et al. 2016]. DH response at exercise iso-time was calculated as the difference in IC between pNIV and PLB (i.e.: IC pNIV – IC PLB - a positive value indicating improvement with pNIV).

Patients who showed a clinically significant increase in IC (≥4.5% of predicted resting IC [O'Donnell, et al. 2001b]) when using pNIV compared to the PLB technique at exercise iso-time were identified as 'DH responders'. Patients showing a less than the clinically significant increase, or a decrease, in IC using pNIV compared to PLB were defined as 'DH non-responders'. Independent sample t-tests were carried out to compare variables between responders and non-responders for the baseline demographic and lung function characteristics. Two-way ANOVA with repeated measurements followed by least significant difference (LSD) post-hoc analysis was employed to compare physiological changes at exercise iso-time between pNIV and PLB techniques in both responders and non-responders. The results of the questionnaire between responders and non-responders were analysed by the Wilcoxon singed-rank test and presented as median (IQR). The level of significance for all analyses was set at $p<0.05$.

3. Results

The baseline characteristics of the patients are presented in table 1. Based on the DH data at exercise iso-time, 8 participants were identified as 'DH non-responders' to pNIV, whilst the remaining 16 participants were deemed as 'DH responders' to pNIV. Responders exhibited a tendency for greater FEV_1, FVC, and resting IC compared to the non-responders. In addition, RV/TLC% was greater ($p=0.028$) in DH non-responders compared to DH responders, indicating greater resting hyperinflation and mechanical restriction to tidal volume expansion (Table 1).

In DH non-responders, exercise endurance time was not different when using the pNIV device (30.9±3.4 min) compared to PLB (29.9±3.3 min) ($p=0.603$). In DH

responders, exercise endurance time was significantly greater (p=0.001) with pNIV (34.9±2.4 min) compared to PLB (27.1±2.3 min) (Figures 2c & 2d & Table 2).

At exercise iso-time in DH non-responders IC was 240±40 ml (p=0.001) lower with pNIV compared to PLB, whilst IC was 220±50 ml (p=0.001) greater in DH responders (Figure 2a & 2b & Table 2), (p=0.001) as expected. Across all 24 patients, the magnitude of change in exercise tolerance with pNIV compared to PLB was associated with the magnitude of change in DH (r=0.46, p=0.022) (Figure 3a). Furthermore, resting DH (inferred by RV/TLC %) was negatively associated with the magnitude of exercise-induced DH when using pNIV compared to PLB (r=-0.42, p=0.043) (Figure 3b).

At exercise iso-time use of pNIV compared to PLB reduced breathlessness by a clinically meaningful margin (by 1.3±0.3 units, p=0.001) in DH responders [Puente-Maestu, et al. 2016,O'Donnell, et al. 2018]. In DH non-responders the reduction in breathlessness, measured by Borg scale, with the use of pNIV compared to PLB (by 0.6±0.5 units, p=0.118) was not clinically meaningful. In addition, use of pNIV compared to PLB reduced leg discomfort in both DH responders and non-responders (by 0.6±0.2 units, p=0.026 and by 0.8±0.3 units, p=0.034, respectively), albeit by non-clinically meaningful margins [Jones, et al. 2014].

In DH responders, application of pNIV compared to PLB reduced minute ventilation (by 1.0±0.8 L, p=0.224) due to lower breathing frequency (by 1±1 breaths.min^{-1} p=0.216), whilst tidal volume was increased (by 0.1±0.02 L, p=0.018) (Table 2). In contrast, in DH non-responders pNIV compared to PLB increased minute ventilation (by 2.7±1.1 L, p=0.021) secondary to increased breathing frequency (by 2±1

breaths.min^{-1}, p=0.046), whilst tidal volume was unaffected (Table 2). Thus, there was a significant difference in the breathing pattern of response between DH responders and DH non-responders with pNIV compared to PLB in minute ventilation (p=0.012), breathing frequency (p=0.026) and tidal volume (p=0.046).

At exercise iso-time, the fraction of tidal volume to inspiratory capacity (V_T/IC %) was increased in DH non-responders (by 6±2%, p=0.001) with the use of pNIV compared to PLB, whereas it was decreased (by 3±1%, p=0.010) in DH responders (Table 2). In addition, in DH non-responders there was a reduction in inspiratory time (by 0.1±0.03 sec, p=0.017) and expiratory (by 0.2±0.1 sec, p=0.010) time, and total duty cycle (by 0.3±0.1 sec, p=0.008) with the use of pNIV compared to PLB (Table 2). There were no differences between pNIV and PLB in duty cycle in DH responders (Table 2). Thus, there was a significant difference in the pattern of response between DH responders and non-responders with pNIV compared to PLB in inspiratory time (p=0.004, expiratory time (p=0.004) and duty cycle (p=0.002).

There were no differences in stroke volume and heart rate with pNIV compared to PLB in either of the groups (Table 2). However, in DH responders cardiac output was greater with pNIV compared to PLB (by 0.6±0.3 L.min^{-1}, p=0.035) (Table 2), whereas cardiac output was not different between pNIV and PLB in DH non-responders.

Compared to the pre-VitaBreath period, at 12 weeks DH responders were significantly less anxious about becoming breathless on a 10-point Likert Scale: (median (IQR) pre-VitaBreath=7.31 (5.25–9.75); 12 weeks=3.75 (2.00–5.75); (p=0.001) and 11 of 16 patients perceived a shorter time to recovery from breathlessness (p=0.004) (Table 3). In contrast, compared to the pre-VitaBreath

period, at 12 weeks in DH non-responders there was a trend to be less anxious about becoming breathless (pre-VitaBreath=6.88 (6.00–8.00); 12 weeks=4.75 (2.25–7.25); (p=0.127) and 5 of 8 patients perceived a shorter time to recovery from breathlessness (p=0.034) (Table 3).

4. Discussion

The main finding of this analysis was that only DH responders showed an improvement in exercise tolerance with pNIV compared to PLB. DH non-responders showed similar exercise tolerance with pNIV and PLB. Compared to DH responders, DH non-responders had greater resting DH, thus greater mechanical restriction to tidal volume expansion during exercise, and tended towards more severe airflow obstruction. The application of pNIV worsened ventilatory responses in DH non-responders, who adopted a more tachypnoeic breathing pattern, but improved the ventilatory response in DH responders.

Our findings within DH responders are supported by previous research into different NIV modes as an adjunct to exercise training, where increases in exercise tolerance similar to the present study are reported [Ambrosino and Cigni 2015,Ambrosino and Xie 2017]. Lack of improvement in exercise endurance time in DH non-responders may be attributed to the failure of pNIV to reduce DH and thus relieve symptoms of breathlessness. There is strong evidence that a reduction in the mechanical restriction to tidal volume expansion is closely related to a reduction in symptoms of exertional breathlessness [O'Donnell, et al. 2018,Laviolette and Laveneziana 2018,Neder, et al. 2019]. Additionally, a study by Fröhlich and colleagues reported that exercise capacity was significantly lower in patients with greater baseline

RV/TLV compared to patients with lower RV/TLC [Fröhlich, et al. 2019]. These findings are further supported by the study of Neder and colleagues that reported that in patients with COPD, the lower the end-expiratory lung volume over the total lung capacity ratio is (and thus, the RV/TLC) the greater the exercise tolerance [Neder, et al. 2019]. Therefore, the potential mechanism explaining the lack of improvement in exercise tolerance in DH non-responders when using pNIV compared to PLB is probably the failure to alleviate such mechanical constraints [O'Donnell, et al. 2018,Laviolette and Laveneziana 2018,Neder, et al. 2019], and subsequently to reduce symptoms of breathlessness by a clinically meaningful amount (>1.0 on a Borg 1-10 scale) as observed with the DH responders [Puente-Maestu, et al. 2016].

DH is an important factor limiting exercise tolerance in patients with COPD [O'Donnell, et al. 2001b,O'Donnell, et al. 2018,Laviolette and Laveneziana 2018]. Compared to DH responders, DH non-responders tended to have a lower FEV_1, which is associated with increased lung volumes and greater lung hyperinflation at rest [O'Donnell, et al. 2001b]. These findings are consistent with advanced COPD with emphysema [Bailey 2012].. Although both groups exhibited a reduction in Borg scale breathlessness when using pNIV, only DH responders achieved a clinically meaningful reduction (>1.0 units) [Puente-Maestu, et al. 2016]. In COPD, DH causes inspiratory muscle shortening and tidal volume constraints, effecting ventilatory and central motor output [Laviolette and Laveneziana 2018,O'Donnell and Laveneziana 2007] and thus increasing work of breathing and consequent breathlessness.

The reduction in the magnitude of DH when using pNIV compared to PLB in DH responders is most likely associated with the greater ability to expand tidal volume during exercise, resulting in improved ventilatory coupling and subsequent reduction in breathlessness [Laviolette and Laveneziana 2018,O'Donnell and Laveneziana 2007]. Use of pNIV in DH responders was associated with an increase tidal volume with lower breathing frequency, increasing the duty cycle. These findings are in accordance with the existing literature showing that even relative small changes in tidal volume and breathing frequency are associated with reduced breathlessness during constant load exercise at 75% of WRpeak following bronchodilator therapy [Peters, et al. 2006]. In contrast, the more tachypnoeic breathing pattern adopted by DH non-responders resulted in less expiratory time and thus increased air trapping and exacerbated breathlessness [O'Donnell, et al. 2018,Laviolette and Laveneziana 2018,Neder, et al. 2019]. The increased fraction of tidal volume to inspiratory capacity (V_T/IC %) in DH non-responders demonstrates they were more likely to reach the point during exercise where they were unable to further increase tidal volume when using pNIV compared to PLB (Table 2) [O'Donnell, et al. 2001b]. It is possible that in some subjects the fixed EPAP was insufficient to overcome flow limitation, thus failed to facilitate expiration, or that excessive pressures directly worsening DH. Use of self-adjusting EPAP tailored to the individual patient may lead to better outcomes.

A recent study by Souza and colleagues [Souza, et al. 2019] reported that application of bi-level Positive Airway Pressure -BiPAP (IPAP: 15 cmH_2O, EPAP: 5 cmH_2O) in moderate COPD reduced operational lung volumes and breathlessness, increasing exercise tolerance at different levels of exercise. However, in contrast to the present

study, BiPAP was applied throughout exercise and IPAP and EPAP pressures were tailored to a level that was comfortable to the individual patient [Souza, et al. 2019]. The VitaBreath device delivers fixed pressures of 18 cmH_2O inspiratory pressure and 8 cmH_2O expiratory pressure. For NIV to be beneficial in COPD patients, the external positive end-expiratory pressure (PEEPe) provided by the ventilator must match the patients intrinsic PEEP (PEEPi) [Mora Carpio and Mora 2019]. The fixed pressures of VitaBreath are in contrast to other commonly used, adjustable, NIV methods, and it is likely that the pressures provided by the pNIV device were excessive for the DH non-responders [Cain, et al. 2019]. A study by Nava and colleagues reported that application of PEEPe greater that PEEPi significantly increased end-expiratory lung volumes [Nava, et al. 1993]. In the present study, 8 patients exhibited greater DH, whilst 16 patients experienced less DH with pNIV compared to PLB. Although PEEPi was not assessed in this study, the level of PEEPe (8 cmH_2O) provided by the VitaBreath device was suboptimal compared to the intrinsic PEEPi levels of 2.5cmH_2O reported in the literature for patients with similar severity of COPD to those in the present study, most likely worsened DH in our DH non-responders [Nava, et al. 1993]. Furthermore, when intrinsic and extrinsic PEEP matching is suboptimal, there is increased risk of developing patient-ventilator asynchrony [Milesi, et al. 2017], resulting in increased work of breathing, poor alveolar ventilation and insufficient gas exchange [Tams, et al. 2013]. This supports our view that the ability to match PEEPe to the individual patient's needs in future pNIV devices should improve synchrony and lead to a greater reduction in exercise induced DH, thus improving exercise tolerance and breathlessness.

A potential factor facilitating DH responders to increase their exercise tolerance is the greater BMI compared to DH non-responders. A review by O' Donnell et al., [O'Donnell, et al. 2014] suggested that increased BMI is associated with increased airway resistance and work of breathing in patients with COPD at rest. Moreover, the same study presents lower DH in obese COPD patients compared to normal weight patients with the same disease severity during an incremental cardiopulmonary exercise test [O'Donnell, et al. 2014]. The authors concluded that the respiratory muscles in obese patients with COPD might have a mechanical advantage compared to normal weight patients with the same disease severity, due to the greater absolute IC and the lower operating lung volumes during exercise [O'Donnell, et al. 2014]. This allows obese patients with COPD to perform physical tasks requiring increased ventilation without increased breathlessness [O'Donnell, et al. 2014]. Given the high levels of positive inspiratory and expiratory pressures provided by the VitaBreath device, it is likely that PEEPi and PEEPe were closer matched in patients with high BMI, thereby enchasing the mechanical advantages previously reported during exercise [O'Donnell, et al. 2014].

Only 63% of non-responders reported faster recovery from breathlessness after 12 weeks of using the VitaBreath device compared to 75% of responders. Furthermore, only patients in the DH responders group reported a significant reduction in anxiety related to breathlessness during activities of daily life.

4.1 Study limitations

This is a post hoc analysis and response was defined in terms of DH and not the primary outcome (exercise endurance time) of the original study. Inspiratory and expiratory

positive airway pressures provided by the pNIV device were fixed, therefore adjustment of the aforementioned pressures was not possible. This is distinct to other studies applying NIV in COPD patients given that the level of provided pressure is individualised to maximise the benefit of use. This represents a very important disadvantage of the VitaBreath device, which clearly mitigated the beneficial impact it had on some patients.

4.2 Clinical implications

The findings of the present study suggest that, although pNIV presents with promising results and favourable practical benefits, it is not effective in improving DH in all COPD patients. This may be because the fixed pressures were suboptimal in some of the patients. Further studies in auto-adjusted ventilators are warranted in this population. However, use of self-adjusting EPAP during physical effort has not been demonstrated and this seems complicated due to the actual device algorithm. Considering the variation in response we have reported, it is important that clinicians assess the response to pNIV on an individual basis in order to verify whether using a portable NIV device during rehabilitation or at home makes the patient feeling better or worse. Clinicians may administer a similar questionnaire to patients as the one used in our original study [Vogiatzis, et al. 2019] to evaluate perception of breathlessness when using a pNIV device on an individual basis. The findings of the present study provide evidence that patients who cannot tolerate continuous NIV methods during exercise, may use the NIV apparatus in recovery from exercise when an intermittent mode of exercise is undertaken. This approach will facilitate the majority of patients to recover from breathlessness faster, thereby increasing the

number of intermittent exercise bouts that they can endure in the setting of pulmonary rehabilitation.

5. Conclusions

Application of pNIV during the recovery from intermittent exercise improves exercise tolerance and breathlessness in the majority of COPD patients. However, this is not the case in patients with profound resting dynamic hyperinflation and ventilatory constraints during exercise.

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Table 1 Patient Demographic data

	DH Non-responders (n=8)	DH Responders (n=16)	p
Gender (M/F)	4/4	6/10	
Age (years)	67±3	67±2	0.934
BMI	24.4±3.1	27.2±1.5	0.363
FEV_1 (litres)	0.96±0.20	1.23±0.16	0.297
FEV_1 (% predicted)	40±8	49±4	0.292
FVC (litres)	2.57±0.35	2.78±0.20	0.594
FVC (% predicted)	86±7	91±5	0.590
FEV_1/FVC	37±5	43±3	0.298
FRC (% predicted)	188±14	166±12	0.288
RV (% predicted)	218±20	198±17	0.470
TLC (% predicted)	135±6	128±7	0.564
IC (% predicted)	70±7	84±6	0.164
IC/TLC (%)	24±3	30±2	0.047
RV/TLC (%)	65±4	56±2	0.028
DLco (litres)	2.60±1.01	3.17±0.44	0.556
DLco (% predicted)	33±11	40±5	0.494
WRpeak (% predicted)	41±8	48±6	0.471
VO_2peak (%predicted)	59±7	61±4	0.722

M, male; F, female; BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FRC, functional residual capacity; RV, residual volume; TLC, total lung capacity; IC, inspiratory capacity; DLco, transfer factor of the lung for carbon monoxide; WRpeak, peak work rate; VO_2peak, peak oxygen uptake; values presented as mean ± standard error of the mean (SEM).

Table 2. Ventilatory and circulatory responses with the use of PLB or pNIV at exercise iso-time in DH non-responders and DH responders

	DH Non-Responders			DH Responders		
	PLB	pNIV	p	PLB	pNIV	p
Endurance time (min)	29.9±3.3	30.9±3.4	0.603	27.1±2.3	34.9±2.4$^{\#}$	0.001
Minute ventilation ($L.min^{-1}$)	28.0±5.8	30.7±5.6	0.021	37.8±4.1	36.8±4.0$^{\#}$	0.224
Tidal volume (litres)	1.0±0.2	1.0±0.2	0.482	1.2±0.1	1.3±0.1$^{\#}$	0.018
IC (litres)	2.14±0.24	1.90±0.25	0.001	2.19±0.17	2.41±0.18$^{\#}$	0.001
V_T/IC (%)	47±3	53±3	0.001	56±2	53±2	0.010
bf ($breath.min^{-1}$)	28±2	30±2	0.046	30±1	29±1$^{\#}$	0.216
Inspiratory time (sec)	0.8±0.1	0.7±0.1	0.017	0.8±0.1	0.8±0.1$^{\#}$	0.059
Expiratory time (sec)	1.5±0.1	1.3±0.1	0.010	1.3±0.1	1.4±0.1$^{\#}$	0.116
Duty cycle (sec)	2.3±0.1	2.0±0.1	0.008	2.1±0.1	2.2±0.1$^{\#}$	0.071
Stroke volume (ml)	88±7	88±6	0.971	95±5	98±5	0.122
Heart rate ($beats.min^{-1}$)	111±6	114±6	0.223	109±4	108±4	0.913
Cardiac output ($L.min^{-1}$)	9.5±0.9	9.9±0.8	0.335	10.3±0.6	10.9±0.6	0.035

PLB, pursed lip breathing; pNIV, portable non-invasive ventilation; V_T, tidal volume; IC, inspiratory capacity; bf, breathing frequency $^{\#}$: significant differences ($p<0.05$) in the pattern of response between the two groups; values presented as mean ± standard error of the mean (SEM).

Table 3. Effect of the use of VitaBreath device on anxiety and recovery from breathlessness in DH responders and DH non-responders

	DH Non-Responders			DH Responders		
Question	**Pre-VitaBreath**	**Post-VitaBreath**	***p*-Value**	**Pre-VitaBreath**	**Post-VitaBreath**	***p*-Value**
How anxious are you about becoming short of breath (SOB)? 1 = Not at all anxious 10 = Very anxious	6.88 (6.00–8.00)	4.75 (2.25–7.25)	0.127 * 6 improvements 1 worse 1 ties	7.31 (5.25–9.75)	3.75 (2.00–5.75)	0.001 * 15 improvements 1 ties
How long did it take you to recover from SOB?			0.034 *			0.004 *
<1 min	0 (0%)	2 (25%)	5 improvements	1 (6.3%)	4 (25%)	11 improvements
2–3 min	3 (37.5%)	3 (37.5%)		3 (18.8%)	6 (37.5%)	1 worse
4–5 min	1 (12.5%)	1 (12.5%)	3 ties	2 (12.5%)	3 (18.8%)	4 ties
5–7 min	2 (25%)	0 (0%)		2 (12.5%)	1 (6.3%)	
7–10 min	0 (0%)	0 (0%)		6 (37.5%)	2 (12.5%)	
More than 10 min	2 (25%)	2 (25%)		2 (12.5%)	0 (0%)	

Data presented as median (IQR) or absolute number (%); *Wilcoxon signed-rank test

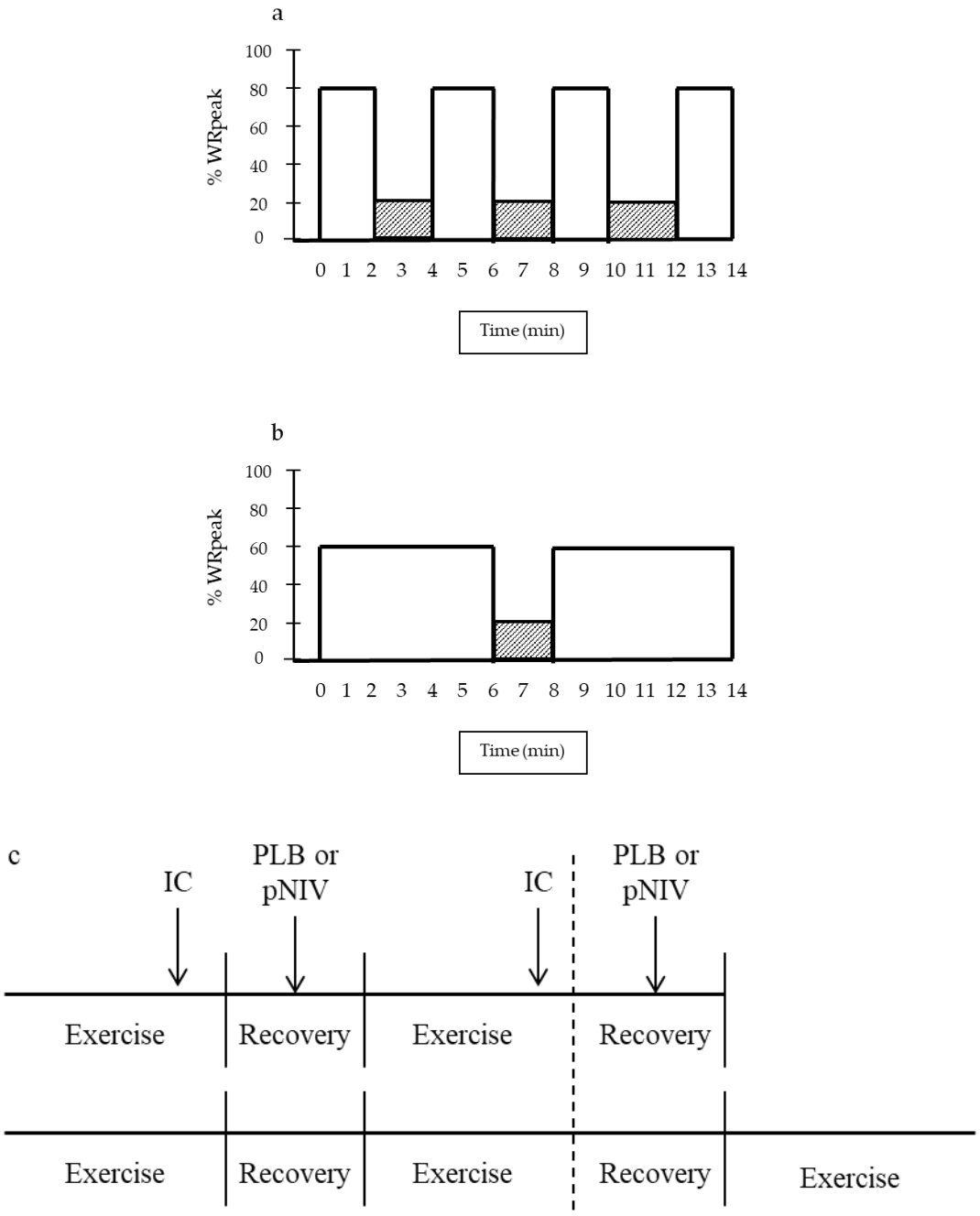

Figure 1. Exercise protocols: (a) High-intensity 2-min exercise / 2-min rest intermittent protocol and (b) moderate-intensity 6-min exercise / 2-min rest intermittent protocol; (c) conceptual representation of the exercise iso-time point, where work completed was consistent between the application of NIV and PLB in both protocols, thereby allowing comparisons to be made that were unaffected by the HI or MOD exercise protocols. Dotted line denotes exercise iso-time where comparisons were made. IC denotes inspiratory capacity manoeuvres, PLB: pursed lip breathing, pNIV: portable NIV.

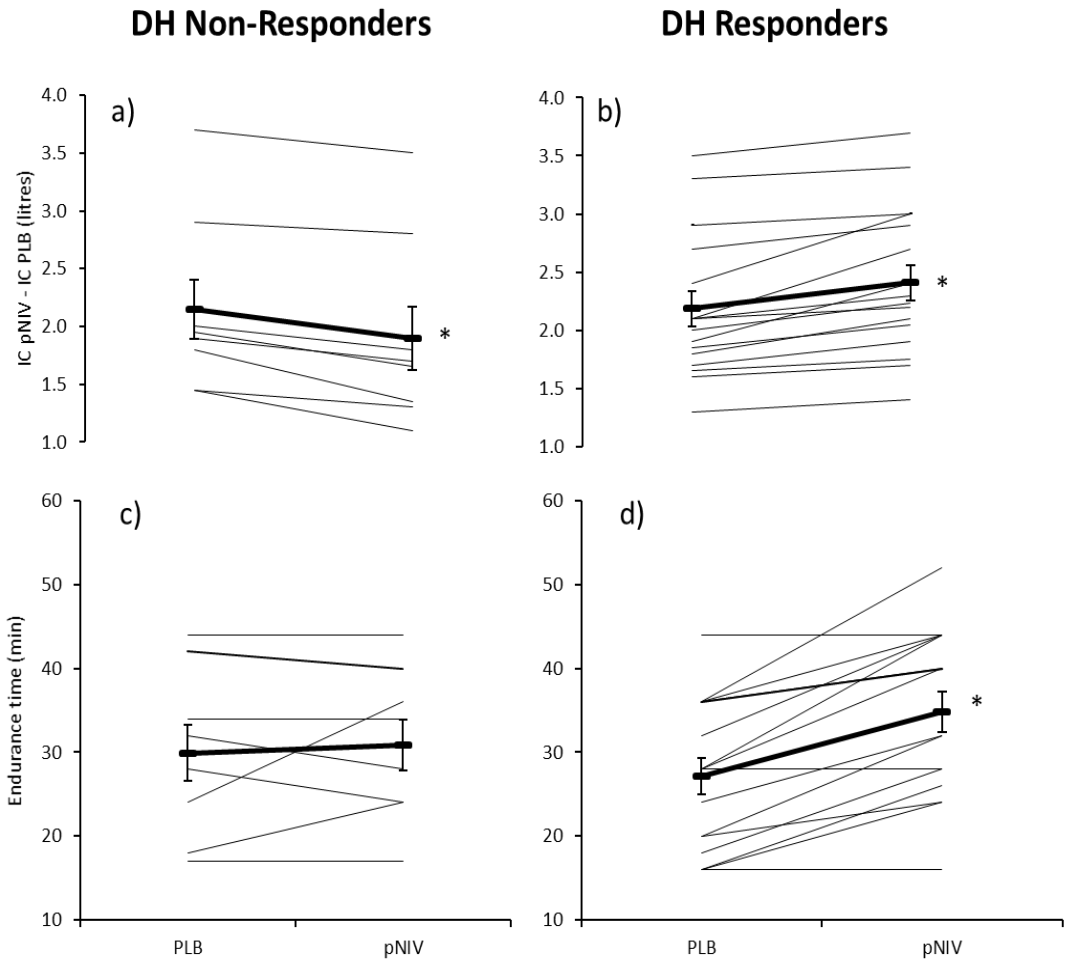

Figure 2. Individual differences in inspiratory capacity (IC) at exercise iso-time (a & b) and in endurance time (c & d) between pNIV and PLB, in DH non-responders (left panel) and DH responders (right panel). Thick lines represent mean±SEM. Asterisks denote significant differences ($p<0.05$) between pNIV and PLB within each group.

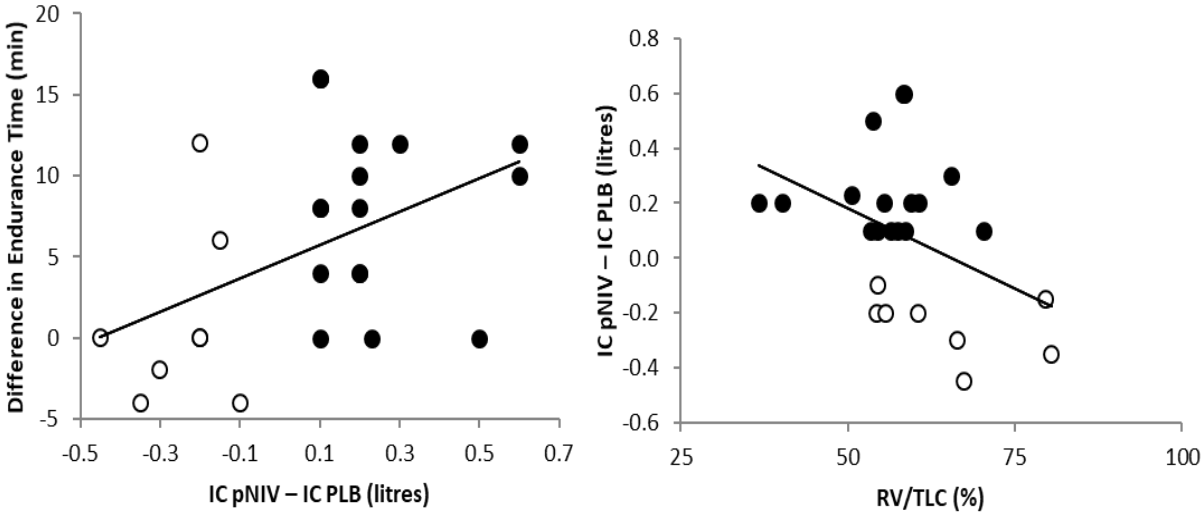

Figure 3. a) Association between differences in endurance time and in inspiratory capacity (IC) between pNIV and PLB application at exercise iso-time (r=0.46, p=0.022) and b) association between differences in IC when using pNIV compared to PLB at exercise iso-time with baseline residual volume as a fraction of total lung capacity ratio (RV/TLC) (r=-0.42, p=0.043). Open symbols denote DH non-responders and closed symbols DH responders.