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Effect of portable non-invasive ventilation on thoracoabdominal volumes in recovery from intermittent exercise in patients with COPD

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Running Head: Effect of portable NIV during recovery from exercise in COPD

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Abstract

Background: We previously showed that use of portable non-invasive ventilation (pNIV) during recovery periods within intermittent exercise improved breathlessness and exercise tolerance in COPD patients compared to pursed-lip breathing (PLB). However, in a minority of patients recovery from dynamic hyperinflation (DH) was better with PLB, based on inspiratory capacity. We further explored this using Optoelectronic Plethysmography to assess total and compartmental thoracoabdominal volumes.

Methods: Fourteen COPD patients (mean±SD) (FEV_1: 55±22% predicted) underwent, in a balanced order sequence, two intermittent exercise protocols on the cycle ergometer consisting of five repeated 2-min exercise bouts at 80% peak capacity, separated by 2-min recovery periods, with application of pNIV or PLB in the first minute of recovery.

Results: Our findings identified 7 patients showing recovery in DH with pNIV (DH responders) while 7 showed similar or better recovery in DH with PLB. When pNIV was applied, DH responders compared to DH non-responders exhibited greater tidal volume (by 0.8±0.3 L, p=0.015), inspiratory flow rate (by 0.6±0.5 L/sec, p=0.049), prolonged expiratory time (by 0.6±0.5 sec, p=0.006) and duty cycle (by 0.7±0.6 sec, p=0.007). DH responders showed a reduction in end-expiratory thoracoabdominal DH (by 265±633 ml) predominantly driven by reduction in the abdominal compartment (by 210±494 ml); this effectively offset end-inspiratory rib-cage DH. Compared to DH non-responders, DH responders had significantly greater BMI by 8.4±3.2 kg/m^2, p=0.022 and tended towards less severe resting hyperinflation by 0.3±0.3 L.

Conclusion: COPD patients who mitigate end-expiratory rib-cage DH by expiratory abdominal muscle recruitment benefit from pNIV application.

Keywords: Exercise, NIV, COPD, Opto-Electronic Plethysmography, Dynamic Hyperinflation

New and Noteworthy

Compared to the pursed-lip breathing technique, acute application of portable non-invasive ventilation during recovery from intermittent exercise improved end-expiratory thoracoabdominal dynamic hyperinflation (DH) in 50% of COPD patients (DH responders). DH responders, compared to DH non-responders, exhibited a reduction in end-expiratory thoracoabdominal DH predominantly driven by the abdominal compartment that effectively offset end-expiratory rib cage DH. The essential difference between DH responders and DH non-responders was, therefore, in the behaviour of the abdomen.

Introduction

Expiratory flow limitation (EFL) is an important pathophysiological hallmark in Chronic Obstructive Pulmonary Disease (COPD), limiting exercise tolerance secondary to increased dynamic hyperinflation (DH) (13, 38). DH is manifested by increased end-expiratory lung volume that reduces inspiratory reserve volume (IRV). This forces COPD patients to breathe close to their total lung capacity (TLC), increasing both work of breathing and breathlessness (38). Additionally, DH may cause adverse central hemodynamic effects by reducing venous return, thus impairing the normal increase in stroke volume and cardiac output during exercise (1, 50). Non-invasive ventilation (NIV) is one of the ergogenic approaches that has been implemented to reduce DH and breathlessness, thus improving exercise tolerance in COPD (3).

A limited number of studies have assessed the effect of NIV on the magnitude of DH during exercise by measuring inspiratory capacity (IC) (38) in patients with COPD with conflicting evidence. Accordingly, application of NIV during exercise has shown to either increase DH (43), or decrease DH (39), albeit the change in IC in the latter study (39) still indicated significant DH above resting values (38). IC manoeuvres are, however, effort dependent and therefore the estimate of DH may be inaccurate, especially during intense exercise.

Application of a portable NIV (pNIV) device (VitaBreath, Philips Respironics Morrisville, PA, USA) was recently shown to increase intermittent exercise tolerance and improve breathlessness in comparison to the pursed lip breathing (PLB) technique in 16/24 COPD patients when applied in the first minute of recovery periods during successive bouts of intermittent exercise (10, 48). VitaBreath is a portable, handheld, battery-powered, pNIV device that provides an expiratory positive airway pressure (EPAP) of 8 cmH_2O and inspiratory positive airway pressure (IPAP) of 18 cmH_2O (17). The VitaBreath device is no longer commercially available, but similar devices may come to market. Nevertheless, the aforementioned studies (10, 48) provided proof of concept on how NIV can be applied intermittently during recovery from exercise in patients with COPD, and how to identify patients most likely to respond to NIV. Furthermore, considering that use of pNIV in activities of daily living improves anxiety around breathlessness, as well as perceived time of recovery from it (48), ventilatory support during recovery from exercise is potentially of value to the COPD patient.

We previously showed that whilst the majority of COPD patients experienced a greater reduction in DH with pNIV compared to PLB (DH responders) based on measurement of IC, in 8/24 of patients the improvement in DH was greater with PLB than pNIV (DH non-responders); it may be that the fixed IPAP and EPAP were suboptimal, at least for DH non-responders (10, 48). Interestingly, DH non-

responders tended to have greater resting airway obstruction and baseline lung hyperinflation, whilst during exercise they exhibited greater restrictions to tidal volume expansion compared to DH responders. Tidal volume expansion during exercise depends on the degree of exercise-induced EFL (12, 18, 33) and the ability to decrease end-expiratory thoracoabdominal volume by recruitment of expiratory abdominal muscles (12, 27, 49). Accordingly, it was suggested that DH responders would represent those patients exhibiting greater capacity to increase tidal volume by recruiting expiratory abdominal muscles (11). However, in our earlier studies (10, 48) we did not assess the degree of expiratory abdominal muscle recruitment. Furthermore, DH was assessed one minute following pNIV and PLB application by performing inspiratory IC manoeuvres (36). Thus, the acute effect of pNIV application on DH was not investigated.

Optoelectronic Plethysmography (OEP) allows breath-by-breath assessment of end-inspiratory and end-expiratory total and compartmental (rib cage and abdominal) thoracoabdominal volumes without the necessity to perform IC manoeuvres (2). The purpose of the present study was to assess total and compartmental thoracoabdominal volumes during acute application of pNIV during recovery from exercise. We hoped to better understand why the rate of recovery from DH is slower with pNIV compared to PLB in DH non-responders compared to DH responders (10, 48).

Earlier work has shown that application of continuous positive airway pressure (CPAP: 7.5-10 cm H_2O) during exercise is associated with inflation of the rib cage compartment with concomitant deflation of the abdominal compartment, secondary to expiratory abdominal muscle recruitment, in the majority of COPD patients (43). Accordingly, it was reasoned that during acute application of pNIV in recovery from intermittent exercise, DH responders would exhibit greater recruitment of expiratory abdominal muscles alongside greater expiratory flow rates when compared to DH non-responders.

Methods

Study design

This was a crossover study investigating the acute effect of pNIV compared to the PLB technique on thoracoabdominal volumes in recovery from intermittent exercise. Central hemodynamic responses, local respiratory muscle oxygen availability and respiratory muscle electromyography activity were also assessed. Patients underwent two sub-maximal intermittent exercise tests sustained at 80% of peak work rate (WRpeak) on a cycle ergometer using both pNIV and the PLB technique during recovery from exercise in a balanced order on the same day. The investigations were carried out following the rules of the Declaration of Helsinki of 1975 (51), revised in 2013. NHS Research Ethics Committee approval (Ref: 19/NE/0091) and Clinical Trials registration (NCT03848819) were obtained. All participants provided written informed consent.

Participants

Inclusion criteria were stable COPD, aged 40 years or older with a smoking history of at least 10 pack years, and who exhibited substantial exercise-induced DH at the limit of incremental cycle exercise tolerance (i.e.: change in inspiratory capacity from baseline >0.15 L or >4.5% of predicted resting IC) (38). Exclusion criteria included COPD exacerbation within 6 weeks prior to exercise testing, unstable comorbidities and inability to exercise.

Baseline Assessment – Visit 1

Prior to exercise testing, participants attended North Tyneside General Hospital for baseline assessment. This included spirometry, body plethysmography lung volume measurements, diffusion capacity, resting electrocardiography (ECG) evaluation, medical history and examination. Following medical assessment, patients performed a ramp incremental exercise test with increments of 5-10 watts every minute to the limit of tolerance on a cycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany) (48) to establish presence of DH (38, 48) and WRpeak.

Intermittent Exercise Protocol – Visit 2

Patients underwent two intermittent exercise protocols on the cycle ergometer (Ergoselect 200, Ergoline GmbH, Bitz, Germany). The exercise protocol consisted of five repeated 2-min exercise bouts at 80% of predefined WRpeak, separated by 2-min recovery periods, to allow application of pNIV or the PLB technique. During the first minute of each recovery period, patients breathed through the pNIV device or adopted the PLB technique. During the second minute of each recovery period patients breathed normally. Before each exercise test patients underwent three-

minutes of baseline measurements (quiet breathing-QB) followed by a three-minute warm-up period with no cycling load.

After the termination of the 5th exercise bout patients underwent 5 minutes of measurements during recovery. Patients performed IC manoeuvres to allow calculation of thoracoabdominal volumes at total lung capacity (TLC) during QB, the second minute of each exercise bout and each recovery period as previously described (40). Total and compartmental thoracoabdominal volumes were recorded by OEP during QB, exercise and recovery periods. Circulatory responses and local respiratory muscle oxygenation were measured non-invasively using impedance cardiography technology and near-infrared spectroscopy, respectively throughout QB, exercise and recovery periods. Electromyography (EMG) activity of respiratory muscles (intercostal, scalene and rectus abdominis) was recorded during the first minute of each recovery period using surface electromyography electrodes. Peripheral oxygen saturation (SpO_2%) was continuously monitored by a pulse oximeter (Onyx Vantage 9590, Nonin Medical Inc, USA). Finally, following each exercise bout dyspnoea and leg discomfort were recorded on the modified 1-10 Borg scale (6).

pNIV and pursed lip breathing

During the first minute of each recovery period in one of the exercise tests, pNIV was applied via the VitaBreath device. The VitaBreath is a portable, handheld, battery-powered, non-invasive ventilation device (pNIV) intended to reduce activity-related shortness of breath (17). It delivers fixed high inspiratory (18 cm H_2O) and expiratory (8 cm H_2O) pressures, but it can only be used during recovery periods interspersing bouts of physical activity.

Patients practiced using the VitaBreath device and the correct adoption of the PLB technique with guidance from a respiratory nurse during the first visit. During the second visit a respiratory physician was present to ensure that patients were able to follow the instructions provided by the researchers and perform the pNIV and PLB techniques correctly.

Thoracoabdominal volumes

During both intermittent exercise tests, thoracoabdominal wall kinematics were assessed by the OEP system (BTS, Milano, Italy) during QB, the second minute of each exercise bout and throughout the recovery periods as follows: the movement of 89 retro-reflective markers placed over the anterior, lateral and posterior chest wall was recorded. Each marker was tracked by eight video cameras (Smart System BTS, Milan, Italy), four in front of the subject and four behind. Subjects used grasp handles positioned at the mid sternum level to lift their arms away from the rib cage

so that lateral markers could be visualised. Dedicated software reconstructed the three-dimensional coordinates of the markers in real time by stereophotogrammetry and calculated total and compartmental thoracoabdominal volume and volume variations using Gauss's theorem. The chest wall was modelled as being composed of two compartments—the rib cage and the abdominal compartments. Total thoracoabdominal volume is the sum of these two compartmental volumes (49).

Circulatory responses

During both intermittent exercise tests, participants were connected to a portable device using impedance cardiography technology (Physio Flow, Enduro, PF-07, Manatec Biomedical, Folschviller, France). The validity of cardiac output recordings using Physio Flow, in comparison to the dye dilution method and the direct Fick method, has been confirmed in both healthy subjects and those with cardiorespiratory disease (9, 26, 46). Cardiac output (CO), heart rate and stroke volume were recorded continuously as previously detailed (34). Six electrodes were placed on patients, two on the left carotid artery (Z1 and Z2), two in the breast area (EKG1 and EKG2) and two in the chest area [Z3 and Z4-EKG3 (neutral)] (34).

Local respiratory muscle oxygen availability

Local respiratory muscle oxygen availability of the intercostal muscles (7^{th} intercostal space) and rectus abdominis was assessed throughout QB, exercise and recovery periods by a NIRO 200 spectro-photometer (Hamamatsu Photonics KK, Hamamatsu, Japan). The NIRO 200 uses Spatially Resolved Spectroscopy method to detect changes in Tissue Oxygenation Index (TOI), Oxygenated haemoglobin (HbO_2), and Deoxygenated haemoglobin (HHb) and its validity has been previously established (29). Two sets of NIRS optodes were placed, one on the skin over the 7th left intercostal space at the midaxillary line and the other over the left rectus abdominis. The optode separation distance was 4 cm, corresponding to a penetration depth of approximately 2 cm. The left intercostal and rectus abdominis were used in order to avoid potential blood flow contributions from the liver (25). NIRS values were zeroed at the start point of each exercise protocol. NIRS data were sampled at 6 Hz and exported in document file format and averaged for offline analysis at 60 s intervals.

Respiratory muscle electromyography

EMG was used to assess respiratory muscle activation during application of pNIV or PLB. Prior to placement of electrodes, the skin was cleaned. Surface electrodes (Delsys Trigno, Delsys, Boston, MA, USA) were placed as previously been described (8) on the surface over the right seventh intercostal space, 2 cm lateral to the umbilicus, over the muscle mass of rectus abdominis and over the scalene muscle.

EMG data were recorded during quiet breathing and at the first minute of each recovery period when pNIV or PLB were applied for 30 seconds. Finally, EMG data were recorded at 2000Hz and were filtered at 25–500 Hz during each trial (Spike 2, Cambridge Electronic Design, Cambridge, UK) (8). All EMG was processed using custom written scripts in Matlab (The Mathworks, Inc. Natick, MA, USA). Data are presented as fractional change in electromyographic activity from baseline values.

Statistical analysis

Estimation of sample size within each breathing modality (i.e. pNIV and PLB) was based on the results of our previous study (48). Using the minimum clinically important difference in DH assessed by inspiratory capacity manoeuvres defined as 4.5% of predicted resting IC (mean: 120 ml within our previous cohort) and observed SD: 110 ml (48), an alpha significance level of 0.05 (2-sided) and 80% power, a minimum total sample size of 13 patients was required. Fourteen patients were recruited in order to achieve balance in the order that the pNIV and PLB trials were performed. Seven patients had previously participated in a study undertaken by our group (48). Data are presented as mean ± standard deviation (SD) unless otherwise stated. DH responders were identified as patients showing a reduction in end-expiratory thoracoabdominal volume with pNIV at least 120 ml greater than that seen with PLB at the first minute of recovery, whereas DH non-responders were those failing to show this degree of response with pNIV compared to PLB (10). The 120 ml dichotomous value was based on our earlier study (10) indicating that patients showing an reduction in DH ≥ 120 ml (40) when using pNIV compared to the PLB technique were identified as DH responders. Patients showing a decrease in DH < 120 ml, or an increase,in DH using pNIV compared to PLB were defined as DH non-responders. Independent sample t-tests were employed to compare baseline characteristics between DH responders and DH non-responders. Two-way repeated measures ANOVA followed by least significant difference (LSD) post-hoc analysis was employed to assess differences in total and compartmental thoracoabdominal volumes, breathing pattern, circulatory responses and local respiratory muscle oxygenation between both the pNIV device and PLB exercise tests, and between DH responders and DH-non responders. Activation of respiratory muscle EMG activity is presented as percentage of change from baseline (QB) and was analysed using paired sample t-tests. Data present mean values for thoracoabdominal and compartmental volumes, circulatory responses, local respiratory muscle oxygen availability, and respiratory muscle EMG activity for: QB, the 5 exercise bouts, the 1st and 2nd minutes of all 5 recovery periods as well as the 3rd, 4th and 5th minute of recovery following the final exercise bout. The level of significance for all analyses was set at $p < 0.05$.

Results

Overall, patients had moderately severe airway obstruction and significant lung hyperinflation at rest (Table 1). Peak exercise capacity was severely impaired; patients exhibited exercise-induced DH and low peak oxygen consumption at the limit of tolerance (Table 1). DH responders had significantly greater BMI and inspiratory flow rate at rest (Table 1).

Thoracoabdominal volumes for all patients

Across all 14 patients, total end-expiratory and end-inspiratory thoracoabdominal and compartmental volumes were not significantly different during exercise between PLB and pNIV trials (Figure 1). Compared to QB, end-expiratory thoracoabdominal volume increased by an average of 266±152 ml during exercise indicating presence of DH (38). Thoracoabdominal IRV at the end of exercise was on average 645±439 ml (Figure 1a). Compared to QB at the end of exercise we found an average increase of 326±291 ml (p=0.001) in thoracoabdominal volume at TLC (Figure 1a).

With acute pNIV application in the first minute of recovery total end-inspiratory thoracoabdominal volume was greater compared to PLB application (by: 230±207 ml; p=0.047) (Figure 1a), secondary to greater end-inspiratory rib cage volume (by: 266±196; p=0.005) (Figure 1b). Total end-expiratory thoracoabdominal volumes were not different (p=0.673) between acute PLB and pNIV applications in the first minute of recovery (Figure 1a). During pNIV application there was a greater increase in end-expiratory rib cage volume (by 198±185 ml p=0.047 value) (Figure 1b) compared to PLB, which was partially compensated by the lower end-expiratory abdominal volume (by 141±124 ml p=0.022) (Figure 1c). IRV (relative to TLC at the end of exercise) was on average 257±227 (p=0.038) ml lower with acute pNIV application compared to PLB, indicating ventilatory constraints (36). At the 5^{th} minute of recovery following the last exercise bout, neither end-inspiratory nor end-expiratory total thoracoabdominal volumes returned to levels recorded during QB (Figure 1a).

Thoracoabdominal volumes during exercise

During exercise total end-expiratory thoracoabdominal volumes were not different (p>0.05) between pNIV and PLB trials for DH responders and DH non-responders, (Figure 2). DH responders and DH non-responders exhibited an increase in end-expiratory thoracoabdominal volume (by: 281±135 ml and by: 248±161 ml, respectively) compared to QB, indicating exercise-induced DH (38) (Figure 2a & 2d). However, DH responders significantly decreased (p<0.05) end-expiratory abdominal volume during exercise compared to QB in both trials (Figure 2c), whereas DH non-

responders maintained end-expiratory abdominal volume unchanged from QB in both trials (p>0.05) (Figure 2f). Exercise IRV was not different (p=0.391) between DH responders (644±513 ml) and DH non-responders (528±353 ml) (Figure 2a & 2d). During exercise DH responders exhibited greater inspiratory and expiratory flow rates compared to DH non-responders (Figure 3 a & 3b).

DH responders in recovery from exercise

Our analysis identified 7 patients as DH responders and 7 patients as DH non-responders (Table 1). In DH responders, during acute application of pNIV compared to PLB, total end-expiratory thoracoabdominal volume was lower by 209±422 ml (38) (Figure 2a), secondary to significantly lower end-expiratory abdominal volume with pNIV compared to PLB (by: 219±197 ml; p=0.026) (Figure 2c), thereby indicating greater expiratory abdominal muscle recruitment. In DH responders during acute application of pNIV compared to PLB, numerical differences did not reach statistical significance for total end-inspiratory thoracoabdominal volume (by 224±465 ml; p=0.250) (Figure 2a) consequently to differences in end-inspiratory rib cage volume (by 186±368 ml; p=0.230) (Figure 2b). IRV with pNIV tended to be lower (p=0.078) compared to PLB (by 302±421 ml) (Figure 2a and Table 2). At the 5th minute of recovery following the last exercise bout, neither end-inspiratory nor end-expiratory total thoracoabdominal volumes returned to levels recorded during QB (Figure 2a).

DH non-responders* in *recovery from exercise

In DH non-responders, during acute application of pNIV compared to PLB, total end-expiratory thoracoabdominal volume was greater (p=0.001) by 356±153 ml (Figure 2d) secondary to greater end-expiratory rib cage volume with pNIV compared to PLB (by: 416±86; p=0.001) (Figure 2e) and unchanged end-expiratory abdominal volume (Figure 2f). During acute application of pNIV total end-inspiratory thoracoabdominal volume was greater compared to PLB (by: 238±218 ml; p=0.047) (Figure 2d), secondary to greater end-inspiratory rib cage volume (by: 346±199 ml; p=0.004) (Figure 2e). There was no significant difference in IRV between pNIV and PLB application (p=0.252) (Figure 2d and Table 2). At the 5th minute of recovery following the last exercise bout, neither end-inspiratory nor end-expiratory total thoracoabdominal volumes returned to levels recorded during QB (Figure 2d).

Differences between DH responders and non-responders in recovery from exercise

Considering pNIV application alone, DH responders compared to DH non-responders exhibited a reduction in end-expiratory thoracoabdominal DH (by 265±633 ml) predominantly driven by reduction in the abdominal compartment (210±494 ml), thereby effectively offsetting end-inspiratory rib cage DH.

Breathing pattern in DH responders and DH non-responders

DH responders: During acute pNIV application compared to PLB, DH responders had greater minute ventilation (by: 6.5±6.4 L/min; p= 0.009), secondary to greater tidal volume (by: 0.5±0.4 L; p=0.002) without any differences in breathing frequency, inspiratory and expiratory time, or duty cycle (Table 2). During acute pNIV application compared to PLB, DH responders exhibited greater inspiratory flow rate (by: 0.4±0.3 L/sec; p=0.001) and greater expiratory flow rate (by: 0.2±0.2 L/sec; p=0.048) (Figures 3a & 3b, Table 2). There were no differences either in average values for breathlessness (p=0.745) or in leg discomfort (p=0.880) between pNIV and PLB application in DH responders (Table 2).

DH non-responders: Compared to PLB, with acute pNIV application DH non-responders increased their minute ventilation (by: 5.7±4.5 L/min; p=0.018) by adopting a more tachypnoeic breathing pattern (compared to DH responders) as breathing frequency was greater with pNIV compared to PLB (by: 7±6 breaths/min; p=0.002) (Table 2). The tachypnoeic breathing pattern resulted in lower inspiratory time (by: 0.3±0.2 sec; p=0.019), lower expiratory time (by: 0.8±0.6 sec; p=0.001) and lower total duty cycle (by: 1.1±0.8 sec; p=0.001) with pNIV application compared to PLB (Table 2). Moreover, with pNIV application compared to PLB there was a trend for greater inspiratory flow rate (by 0.2±0.2 L/sec p=0.064), whilst expiratory flow rate was significantly greater (by: 0.2±0.2 L/sec; p=0.011) (Figures 3a & 3b, Table 2). Following acute application of pNIV compared to PLB breathlessness was lower in DH non-responders (by: 1.1±0.9; p=0.001), whilst leg discomfort was unaffected (p=0.203) (Table 2).

Differences in breathing pattern between DH responders and DH non-responders

When pNIV was applied, DH responders compared to DH non-responders exhibited greater tidal volume (by 0.8±0.5 L, p=0.015), inspiratory flow rate (by 0.6±0.5 L/sec, p=0.049), prolonged expiratory time (by 0.6±0.5 sec, p=0.006) and duty cycle (by 0.7±0.6 sec, p=0.007) whilst breathing frequency was lower (p=0.019) (Table 2).

With pNIV application numerical differences for expiratory flow rate in DH responders compared to DH non-responders (by 0.2±0.5 L/min) did not reach statistical significance (p=0.389). IRV relative to end-exercise TLC during acute pNIV application was not different between DH responders and DH non-responders (p=0.968) (Figures 2a and 2d).

Central haemodynamic responses

CO was unaffected by acute pNIV application compared to PLB in both DH responders and DH non-responders (Figure 4c & 4f). However, in DH responders, throughout recovery from exercise, pNIV application resulted in significantly greater

CO compared to PLB (p=0.024) (Figure 4c) and did not return towards baseline at the 5th minute of recovery. In DH non-responders there were no differences in the pattern of response in any of the central haemodynamic variables between pNIV and PLB application in recovery from exercise (Figure 4 d-f), whereas CO returned towards baseline at the 5th minute of recovery.

EMG muscle activity

Surface muscle EMG revealed two different patterns of respiratory muscle activation during recovery from exercise. DH responders exhibited greater inspiratory and expiratory EMG muscle activity (delta of percentages from baseline between conditions) with pNIV application compared to PLB as this was reflected by the greater activation of intercostal (by: 20±16%; p=0.043), scalene (by: 50±33%; p=0.013) and rectus abdominis (by: 67±57%; p=0.014) muscles (Table 3). In contrast, DH non-responders using pNIV compared to PLB exhibited reduced inspiratory (intercostal and scalene) EMG muscle activity, and increased expiratory (abdominal) EMG muscle activity. This was reflected by lower EMG activity of intercostal (by: 32±22%; p=0.009) and scalene (by: 32±30%; p=0.047) muscles and greater EMG activity of rectus abdominis muscle (by: 33±31%; p=0.049) (Table 3). Accordingly, greater EMG activity of the inspiratory muscles during pNIV compared to PLB was evident in DH responders compared to DH non-responders for intercostal (p=0.004) and scalene (p=0.007) muscles. There was no difference in the pattern of rectus abdominis EMG muscle activity between DH responders and DH non-responders with pNIV compared to PLB applications (p=0.538); both DH responders and DH non-responders increased EMG abdominal muscle activity with pNIV compared to PLB (Table 3). However, DH responders exhibited a two fold greater increase in EMG abdominal muscle activity with pNIV compared to PLB in comparison to DH non-responders (Table 3).

Respiratory muscle oxygen availability

In DH responders, when pNIV was applied compared to PLB, deoxygenated haemoglobin was greater in intercostal muscles (by: 2.3±2.1 µmol/L; p=0.048) and rectus abdominis muscle (by: 1.8±1.7 µmol/L; p=0.047). In DH non-responders, pNIV application compared to PLB caused greater levels of deoxygenated haemoglobin in intercostal (by: 2.1±1.5 µmol/L; p=0.040) and rectus abdominis (by: 4.6±4.0 µmol/L; p=0.045) muscles. There were no differences in the pattern and magnitude of response of deoxygenated haemoglobin of intercostal and abdominal muscles between DH responders DH non-responders.

Discussion

Main findings

In line with our earlier studies (10, 48) we have identified two different patterns of DH response to acute application of pNIV compared to PLB in recovery from exercise in COPD: DH responders showing a greater improvement in DH using pNIV compared to PLB of at least 120 ml and DH non-responders failing to show this degree of response with pNIV compared to PLB. When pNIV was applied in recovery from exercise, DH responders compared to DH non-responders exhibited greater tidal volume, inspiratory and expiratory flow rates, prolonged expiratory time and duty cycle, and experienced lower end-expiratory DH secondary to greater expiratory abdominal muscle recruitment. DH responders had significantly greater BMI and resting inspiratory flow rate, and less severe resting hyperinflation compared to DH non-responders.

Study novelties

To the best of our knowledge this is the first study to assess total and compartmental thoracoabdominal volumes acutely during application of a NIV method in recovery from exercise in patients with COPD. Use of optoelectronic plethysmography allowed patients to breathe normally and carry out ventilatory measurements without the need of a valve and mouthpiece. In contrast to our previous studies (10, 48), the present study used optoelectronic plethysmography to assess the magnitude of dynamic hyperinflation in recovery from exercise when using pNIV or PLB without requirement of inspiratory capacity manoeuvres that are effort dependent (1, 2). Finally, use of optoelectronic plethysmography allowed us to evaluate the breathing pattern throughout the application of pNIV and PLB including breath-by-breath recordings of expiratory and inspiratory time and flow rates, total duty cycle, tidal volume, breathing frequency, and minute ventilation.

Differences in baseline characteristics between DH responders and non-responders

One significant difference between DH responders and DH non-responders was elevated BMI presented in the group of DH responders. A recent study (10) argued that a possible mechanism that allowed DH responders compared to DH non-responders to benefit from pNIV was the increased BMI (10). It has previously been reported that the respiratory muscles of COPD with high BMI might have a mechanical advantage in comparison to patients with normal BMI (35). This has been attributed to the increased inspiratory capacity (i.e. lower resting hyperinflation) in patients with high BMI, which was evident in the DH responders in the present study. Moreover, patients with high BMI might have an advantage when using pNIV, which applies a high expiratory positive airway pressure (8 cmH_2O) in comparison to other NIV devices (7, 19, 22, 44, 45, 47). It is known that intrinsic positive end-

expiratory pressure (PEEPi) needs to be closely matched with extrinsic positive end-expiratory pressure (PEEPe) (31). If PEEPe is significantly lower than PEEPi there will be no improvement in operational lung volumes (14, 32). In contrast, if PEEPe is much greater than PEEPi, dynamic hyperinflation will worsen and result in adverse central haemodynamic responses (16, 28). Patients with higher BMI exhibit greater PEEPi (35), thus NIV devices with higher expiratory positive airway pressure (PEEPe), such as the VitaBreath device in the present study (8 cm H_2O), might be better suited to patients with high BMI (10). Future devices may be able to tailor the expiratory pressure to overcome expiratory flow limitation in individual patients.

DH responders

Application of pNIV compared to PLB was associated with increased end-inspiratory rib cage and total thoracoabdominal volumes in DH responders. This finding is explained by the high fixed IPAP (18 cmH_2O) provided by the VitaBreath device, but is in line with other NIV methods showing an inflation of the rib cage compartment with NIV application (43). However, application of pNIV compared to PLB lessened end-expiratory abdominal and total thoracoabdominal volumes in DH responders.

It is well known that COPD patients develop varying degrees of expiratory flow limitation. This leads to DH at different ventilatory levels during exercise, but which greatly differ among patients with COPD (21, 49). Indeed, Vogiatzis and colleagues identified two different DH patterns during exercise and in recovery from exercise, namely early and late DH (49). COPD patients who developed late DH during exercise were those who compensated end-expiratory rib cage DH by expiratory abdominal muscle recruitment (49). When using pNIV, DH responders in the present study exhibited a similar pattern to that previously described for late DH (49); they were able to compensate end-expiratory rib cage DH by recruiting their expiratory abdominal muscles. Furthermore, during exercise and during acute pNIV application, DH responders exhibited greater expiratory flow rates compared to PLB thereby indicating lower degrees of expiratory flow limitation. Presumably, when using pNIV compared to PLB, expiratory abdominal muscle recruitment in conjunction with greater expiratory flow rate and marginally prolonged expiratory time was effective in reducing end-expiratory DH in recovery from exercise (27). Greater expiratory abdominal muscle recruitment with pNIV compared to PLB was in turn corroborated by greater rectus abdominis muscle EMG activity alongside increased rectus abdominis deoxygenated haemoglobin; this suggests greater oxygen extraction due to increased muscle activation.

DH responders were less flow limited during exercise and during acute pNIV application compared to DH non-responders, inferred by the greater inspiratory and expiratory flow rates (Figure 3), allowing them to increase tidal volume more than DH non-responders. Thoracoabdominal tidal volume during acute application of

pNIV was nearly two-fold greater in DH responders than DH non-responders (Table 2). DH responders were able to expand their tidal volume firstly by increasing their end-inspiratory thoracoabdominal volume, and secondly by decreasing their end-expiratory thoracoabdominal volume during acute application of pNIV. This increase in tidal volume was the result of greater thoracoabdominal volume at total lung capacity, allowing a larger increase in end-inspiratory volume up to the point of reaching critical mechanical constraints (Figure 2 a) (38). Greater end-inspiratory thoracoabdominal volume was also associated with greater intercostal and scalene EMG muscle activity and inspiratory flow rates. The increased tidal volume during acute pNIV application was the result of increased abdominal muscle recruitment, which was greater in DH responders compared to DH non-responders (Figure 2c & 2f). This finding is further supported by the EMG data on rectus abdominis showing a two-fold increase in EMG activity with pNIV compared to PLB in DH responders versus DH non-responders. Thus, greater expiratory abdominal power output (the product of their velocity of shortening and the force they develop) in DH responders was expressed more as expiratory flow and less as pressure secondary to lower dynamic airway compression (27). This is most likely the reason why we did not find impaired central hemodynamic responses with pNIV compared to PLB in DH responders. However, greater EMG rectus abdominis muscle activity with pNIV compared to PLB application may account for the lack of difference in dyspnoea levels despite lower DH, given that increased expiratory muscle activity during positive-pressure breathing has been postulated to increase breathlessness (42). Moreover, in DH-responders there was no meaningful difference in dyspnoea between pNIV and PLB. This might be attributed to IRV with pNIV been lower compared to PLB as a result of significantly greater tidal volume expansion with pNIV application (Table 2) (40). Furthermore inspiratory muscle (intercostal and scalene) activity was significantly greater with pNIV compared to the PLB technique (Table 3). Increased inspiratory muscle effort has been shown to be associated with a rise in perceived inspiratory difficulty reflecting increased dissociation between the increased central neural drive and the blunted mechanical response of the respiratory system (23, 37).

DH non-responders

Application of pNIV compared to PLB was associated with increased end-inspiratory and end-expiratory rib cage volumes. However, the increase in end-expiratory rib cage volume was not compensated by a reduction in end-expiratory abdominal volume as reported above for DH responders. This led to an increase in total end-expiratory thoracoabdominal volume and thus DH, which limited tidal volume expansion. In line with our earlier studies (10, 48) tidal volume expansion was

restricted with pNIV compared to PLB application; patients adopted a more tachypnoeic-breathing pattern that reduced inspiratory and expiratory time as well as duty cycle. However, both inspiratory and expiratory flow rates were greater with pNIV compared to PLB secondary to the high fixed airway pressures delivered pNIV.

During pNIV compared to PLB, DH non-responders exhibited greater rectus abdominis EMG activity (and deoxygenated haemoglobin) which, despite the increase in expiratory flow rate, was not successful in mitigating end-expiratory thoracoabdominal DH. This is most likely occurred because in DH non-responders PEEPe did not closely match PEEPi (14), confirming earlier concerns that the fixed IPAP and EPAP were probably suboptimal, at least for DH non-responders (10, 48). DH non-responders may have benefited if the expiratory pressure was automatically tailored to the individual to overcome expiratory flow limitation, whilst avoiding excessive pressures.

Furthermore, inspiratory EMG muscle activity was lower with pNIV compared to PLB as the high inspiratory positive airway pressure (18 cmH_20) was effective in overcoming inspiratory flow limitation, thereby necessitating less effort from the inspiratory muscles. Reduced work of breathing with inspiratory positive airway pressure is possibly associated with lower dyspnoea (20). Interestingly, in DH non-responders, dyspnoea was significantly lower in the pNIV trial compared to PLB. This is attributed to the finding that inspiratory muscle (intercostal and scalene) activity was significantly greater with PLB compared to the pNIV (Table 3), thereby inducing a greater rise in perceived inspiratory difficulty (23, 37).

Thoracoabdominal volumes during exercise and in recovery

In the present study, thoracoabdominal volume at total lung capacity increased from baseline during exercise by an average of 326 ml. This finding is in agreement with a previous study in which COPD patients progressively increased thoracoabdominal volumes at total lung capacity by approximately 200 ml, during a ramp incremental exercise protocol (49). However, despite the fact that patients in the present study performed intermittent submaximal exercise, we report greater increase in thoracoabdominal volumes at total lung capacity compared to that study (49). This might be attributed to the application of pNIV during the recovery periods between exercise bouts, which increased end-inspiratory thoracoabdominal volume in both DH responders and DH non-responders. Importantly, in both DH responders and DH non-responders end-expiratory thoracoabdominal volume did not recover towards quiet breathing by five minutes into recovery. This is in keeping with the studies (41, 49) that found that dynamic hyperinflation 3-5 minutes into recovery from symptom limited exercise was greater than at baseline. The present study extends these findings by showing that in both DH responders and DH non-responders, rib cage hyperinflation during exercise and recovery should have enhanced the threshold

loading of the muscles of the rib cage compartment so that recovery of hyperinflation would take longer to return to baseline (41).

Haemodynamic responses

Previous studies have reported that application of NIV in patients with COPD at rest reduces cardiac output (4, 11). Our short application time of pNIV (1-min) in both DH responders and DH non responders may have prevented adverse circulatory effects; this is in contrast to the existing literature where NIV application exceeded 5 minutes and resulted in adverse circulatory responses (4, 5, 11, 24).

Study limitations

Some outcomes were clinically, but not statistically, significant. This may simply reflect the limited sample size and a definitive outcome may have been achieved in a larger population. The present study was powered to identify differences in the rate of DH between pNIV and PLB. Moreover, we did not measure PEEPi and work of breathing. Measurement of PEEPi could have helped us compare the differences between PEEPe provided by pNIV and the actual PEEPi of DH responders and DH non-responders; this in turn could have potentially further supported the interpretation of our findings. Assessment of the work of breathing would have allowed us compare our findings with the study by Petrof and colleagues (43) who employed CPAP during exercise and further corroborate their findings as we measured respiratory electromyography muscle activity. Although we only recorded the EMG activation of the respiratory muscles during the recovery periods, it is possible that signal could be contaminated by abdominal muscle activation for the purposes of core stabilization whilst sitting on the cycle ergometer. The validity of both surface EMG and NIRS recordings has been previously established (15, 29, 30). Although we ensured that the quality of our measurements was sufficient to include in our analysis, high adipose tissue on the abdomen is possible to have affected the quality of the EMG and NIRS signals.

Furthermore, it is surprising that DH responders showed no difference in breathlessness between pNIV and PLB application. This finding might be due to the fixed duration of exercise as in our earlier study DH responders exercised for longer compared to DH non-responders consequently to lower breathlessness at isotime (10). Interestingly this earlier study from our group showed that in DH responders, use of pNIV during daily activities over a 12-week period made them less anxious about becoming breathlessness compared to DH non-responders (10).

Finally, in contrast to the existing literature using other NIV methods (39, 43) inspiratory and expiratory positive airway pressures were fixed and could not be adjusted for each patient in the present study. Accordingly, DH non-responders may

have responded well to different settings tailored to their physiological needs. Individualized pressure titration using a NIV module with adjustable settings may have provided more useful insight by clarifying whether an optimal pressure setting exists that offers equivalent or superior relief compared to PLB. This technology already exists, has been incorporated in standard home ventilators and could be implemented in future pNIV devices. This warranties further studies to test this possibility. We did not assess the reproducibility of physiological measures during the pNIV and PLB trials to avoid exposure of patients to additional exercise testing.

Clinical implications

The delayed recovery of dynamic hyperinflation following cessation of intermittent exercise has important clinical implications when designing rehabilitative exercise training regimes for patients with severe COPD, particularly if NIV is to be applied only during recovery from exercise. It is apparent from our results that whilst acute pNIV application was effective only in a specific subgroup of patients, clinical characteristics such as baseline hyperinflation can help predict response. Furthermore, COPD patients whose breathing control resembles that of a healthy individual in recruiting expiratory muscles during exercise (1, 50) are more likely to benefit from NIV; they may mitigate rib cage dynamic hyperinflation by expiratory abdominal muscle recruitment. Nevertheless, DH non-responders were less breathless and had greater expiratory flow with pNIV, therefore pNIV was not without some benefit even to this subgroup of patients. During recovery from exercise the improvement in DH lasted only transiently (1-min, during pNIV application) in DH responders. If implementing the use of NIV in the pulmonary rehabilitation setting NIV should perhaps be applied for longer to facilitate complete recovery of DH before moving to a new exercise task. However, 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. An earlier study from our group showed that in DH responders, use of pNIV during daily activities over a 12-week period made them less anxious about becoming breathlessness compared to DH non-responders (10).

Conclusions

COPD patients most likely to benefit from NIV in their recovery from exercise are those who are able, during exercise and in recovery from exercise, to mitigate end-expiratory rib cage dynamic hyperinflation by expiratory abdominal muscle recruitment alongside increased expiratory flow rates.

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Disclosure

The authors declare that they have no competing interests.

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Figures legends

Figure 1. Effect of the application of portable non-invasive ventilation (pNIV) (closed symbols) compared to pursed lip breathing (PLB) (open symbols) on: a) total thoracoabdominal volume, b) rib cage volume and c) abdominal volume in all patients. Circles: end-expiratory volume, triangles: end-inspiratory volume, rhombuses: total thoracoabdominal volume. Grey area highlights acute application of pNIV or PLB. Data are presented as mean ± SEM. QB: quiet breathing, REC: recovery. * $p < 0.05$ pNIV vs PLB.

Figure 2. Effect of the application of portable non-invasive ventilation (pNIV) (closed symbols) compared to pursed lip breathing (PLB) (open symbols) in DH responders (left panel) and DH non-responders (right panel) on: a & d) total thoracoabdominal volume, b & e) rib cage volume and c & f) abdominal volume. Circles: end-expiratory volume, triangles: end-inspiratory volume, rhombuses: total thoracoabdominal volume. Grey area highlights acute application of pNIV or PLB. Data are presented as mean ± SEM. QB: quiet breathing, REC: recovery. * $p<0.05$ pNIV vs PLB, † $p<0.05$ QB vs exercise in end-expiratory volume, §; minimum clinical importance difference between pNIV and PLB.

Figure 3. Effect of the application of portable non-invasive ventilation (pNIV) (closed symbols) compared to pursed lip breathing (PLB) (open symbols) in DH responders (circles) and DH non-responders (triangles) on: a) inspiratory flow rate and b) expiratory flow rate. Data are presented as mean ± SEM. QB: quiet breathing, REC: recovery.* $p<0.05$ pNIV vs PLB, ‡ $p<0.05$ between responders versus non-responders with pNIV.

Figure 4. Effect of the application of portable non-invasive ventilation (pNIV) (closed symbols) compared to pursed lip breathing (PLB) (open symbols) in DH responders (left panel) and DH non-responders (right panel) on: a & d) stroke volume, b & e) heart rate and c & f) cardiac output. Data are presented as mean ± SEM. QB: quiet breathing, REC: recovery. * $p < 0.05$ pNIV vs PLB.

Figure 1

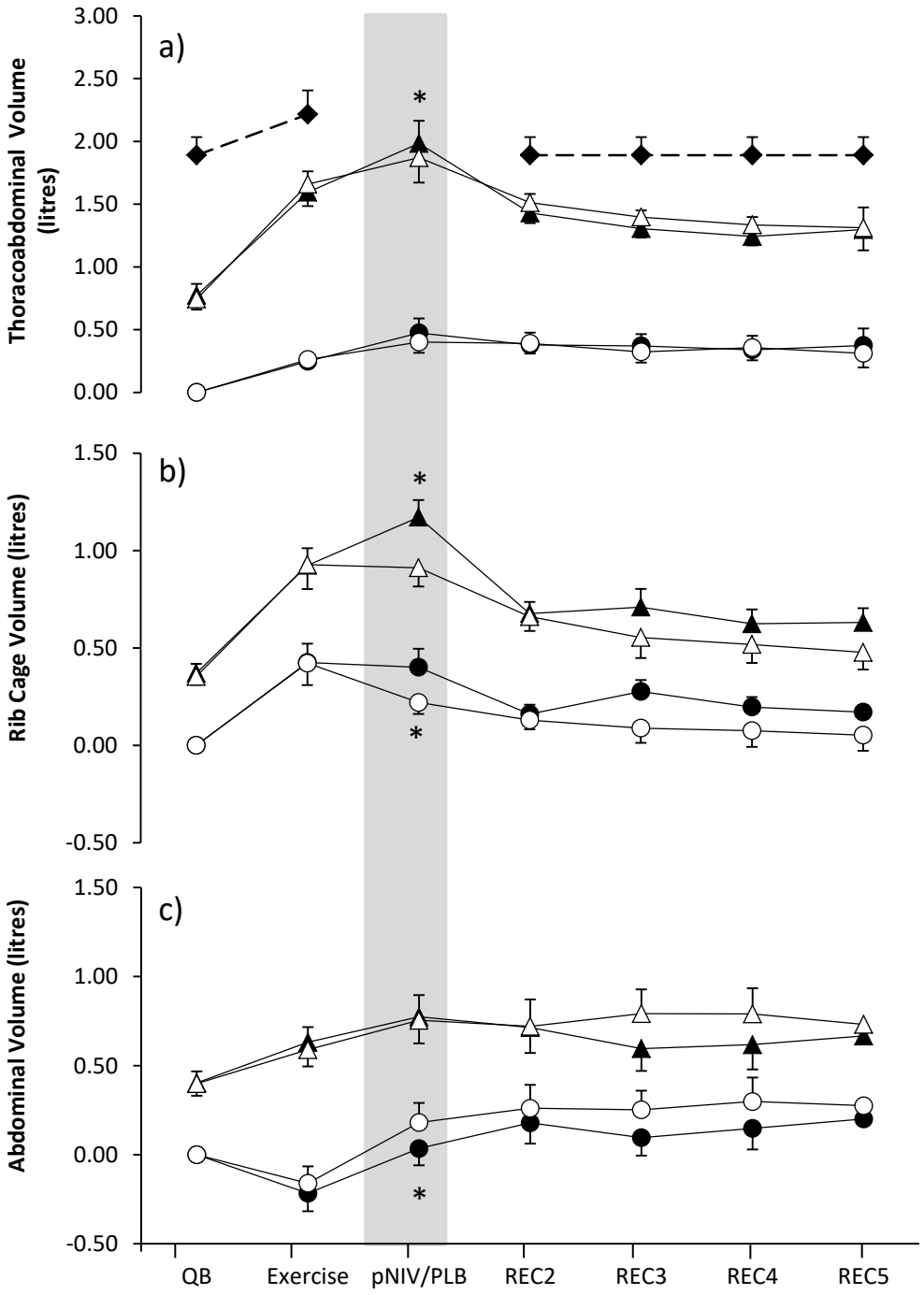
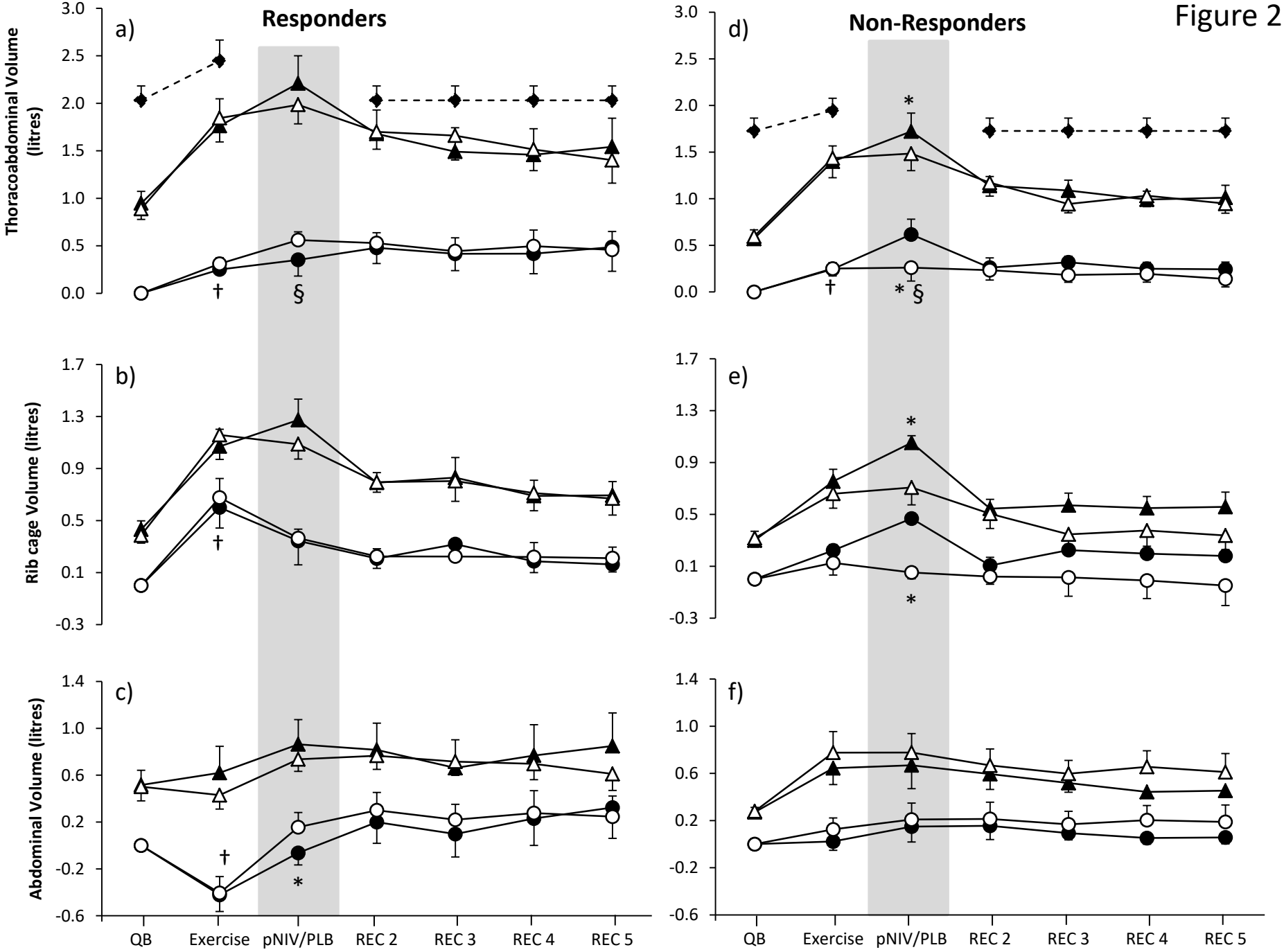

a)
b)
c)
Thoracoabdominal Volume (litres)
Rib Cage Volume (litres)
Abdominal Volume (litres)
3.00
2.50
2.00
1.50
1.00
0.50
0.00
-0.50
*
QB
Exercise
pNIV/PLB
REC2
REC3
REC4
REC5

Figure 2


Responders
Non-Responders
a)
b)
c)
d)
e)
f)
Thoracoabdominal Volume (litres)
Rib cage Volume (litres)
Abdominal Volume (litres)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
1.7
1.3
0.9
0.5
0.1
-0.3
1.4
1.0
0.6
0.2
-0.2
-0.6
†
§
*
QB
Exercise
pNIV/PLB
REC 2
REC 3
REC 4
REC 5

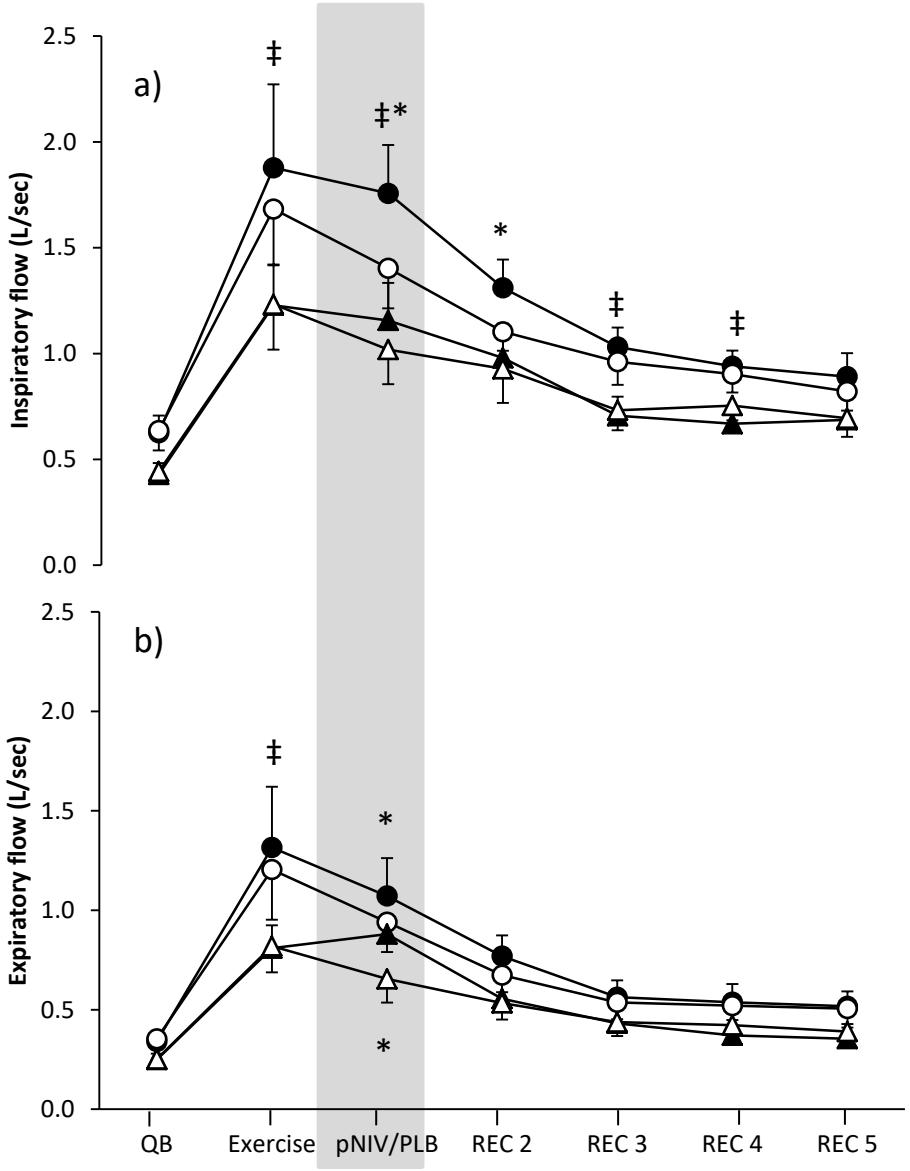

a)
b)
Inspiratory flow (L/sec)
Expiratory flow (L/sec)
2.5
2.0
1.5
1.0
0.5
0.0
‡
‡*
*
‡
‡
‡
*
*
QB
Exercise
pNIV/PLB
REC 2
REC 3
REC 4
REC 5

Figure 4

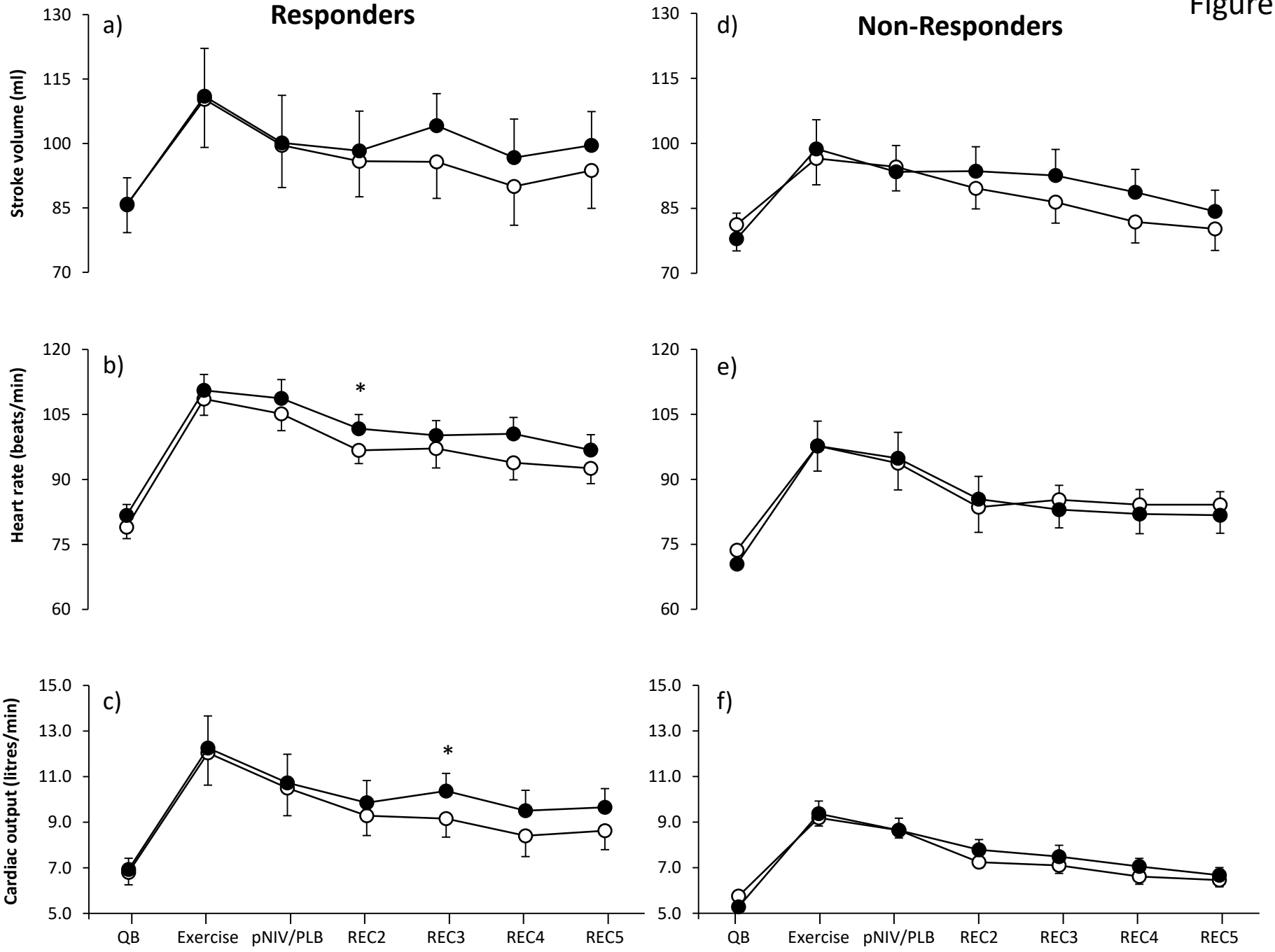

Responders
Non-Responders
a)
b)
c)
d)
e)
f)
Stroke volume (ml)
Heart rate (beats/min)
Cardiac output (litres/min)
130
115
100
85
70
120
105
90
75
60
15.0
13.0
11.0
9.0
7.0
5.0
*
*
QB
Exercise
pNIV/PLB
REC2
REC3
REC4
REC5

Table 1 Patient Demographic data

	All patients (n=14)	DH Responders (n=7)	DH Non-responders (n=7)	p
Age (years)	68.4±8.4	67.7±6.1	69.1±10.7	0.764
BMI (kg/m^2)	28.6±7.2	32.8±6.7	24.4±5.0	0.022
FEV_1 (L)	1.34±0.69	1.53±0.81	1.14±0.53	0.301
FEV_1 (% predicted)	55±22	56±23	54±21	0.861
FVC (L)	2.91±1.07	3.28±1.00	2.53±1.08	0.204
FVC (% predicted)	95±26	93±22	96±31	0.876
FEV_1/FVC	45±13	45±14	45±12	0.984
TLC (% predicted)	126±36	134±41	117±30	0.432
FRC (% predicted)	151±56	167±62	135±50	0.355
RV (% predicted)	173±81	191±93	155±71	0.465
IC (% predicted)	63±18	68±20	58±16	0.319
IC/TLC (%)	35±10	34±8	37±13	0.581
RV/TLC (%)	53±14	53±14	53±15	0.984
DLco (% predicted)	50±19	50±24	49±15	0.930
Inspiratory flow rate (L/sec)	0.5±0.2	0.6±0.2	0.4±0.1	0.042
Expiratory flow rate (L/sec)	0.3±0.1	0.3±0.2	0.3±0.1	0.266
WRpeak (Watts)	56±27	63±31	49±21	0.097
WRpeak (% predicted)	54±30	52±39	56±22	0.778
VO_2peak (% predicted)	71±19	72±19	69±20	0.758
ΔIC peak (ml)	-575±246	-621±173	-529±309	0.501

BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; TLC, total lung capacity; FRC, functional residual capacity; RV, residual volume; IC, inspiratory capacity; DLco, transfer factor of the lung for carbon monoxide; WRpeak, peak work rate; VO_2peak, peak oxygen uptake; ΔIC, change from baseline in inspiratory capacity; values presented as mean ± SD for all baseline characteristics.

Table 2. Breathing pattern and symptoms during acute application of pNIV and PLB

	Responders			Non-Responders		
	pNIV	**PLB**	**p**	**pNIV**	**PLB**	**p**
V_T (L)	1.9±0.7	1.4±0.5	0.002	1.1±0.3*	1.2±0.4	0.369
bf (breaths/min)	21±3	22±5	0.478	27±5*	20±4	0.002
V_E (L/min)	39.0±16.6	32.5±12.4	0.009	29.1±7.6	23.4±9.2	0.018
Ti (sec)	1.1±0.2	1.2±0.3	0.454	1.0±0.2	1.3±0.3	0.019
Te (sec)	1.9±0.4	1.8±0.3	0.765	1.3±0.3*	2.1±0.6	0.001
Ttot (sec)	3.0±0.4	3.0±0.5	0.828	2.3±0.4*	3.4±0.8	0.001
Inspiratory flow rate (L/sec)	1.8±0.6	1.4±0.5	0.001	1.2±0.4*	1.0±0.4	0.064
Expiratory flow rate (L/sec)	1.1±0.5	0.9±0.4	0.048	0.9±0.2	0.7±0.3	0.011
IRV (ml)	200±446	502±477	0.078	240±549	444±246	0.252
Dyspnoea (Borg)	3.1±1.3	3.0±1.3	0.745	2.5±0.7	3.6±1.1	0.001
Leg Discomfort (Borg)	3.8±1.7	3.9±2.0	0.880	3.5±0.9	4.0±1.5	0.203

pNIV: portable non-invasive ventilation, PLB: pursed lip breathing, V_T: tidal volume, bf: breathing frequency, V_E: minute ventilation, Ti: inspiratory time; Te: expiratory time; Ttot: duty cycle time, IRV: inspiratory reserve volume *; $p<0.05$ responders versus non-responders with pNIV application. Data presented as mean ± SD

Table 3. Electromyographic activity of respiratory muscles during acute application of pNIV or PLB

	Responders			Non-Responders		
	pNIV	**PLB**	**p**	**pNIV**	**PLB**	**p**
Intercostal (% baseline)	111±26	91±28	0.043	103±33	135±70	0.009
Scalene (% baseline)	192±81	142±38	0.013	143±43	175±79	0.047
Rectus abdominis (% baseline)	175±126	108±25	0.014	179±140	146±59	0.049

pNIV; portable non-invasive ventilation, PLB pursed lip breathing. Data presented as mean ± SD of the fractional change in electromyographic activity from baseline values

Table 4. Respiratory muscle oxygen availability

	Responders			Non-Responders		
	pNIV	**PLB**	**p**	**pNIV**	**PLB**	**p**
ΔHbO_2 intercostal (µmol/L)	-2.0±4.2	-3.4±3.0	0.120	-1.7±1.6	-2.4±2.1	0.449
ΔHbO_2 abdominal (µmol/L)	0.8±1.0	-0.2±1.5	0.421	0.8±6.2	-3.3±3.9	0.378
ΔHHb intercostal (µmol/L)	3.5±3.0	1.2±1.4	0.048	5.3±3.7	3.2±4.7	0.040
ΔHHb abdominal (µmol/L)	4.6±1.7	2.8±3.8	0.047	3.5±3.3	-1.1±1.8	0.045
ΔTOI intercostal (%)	-3.0±1.9	-4.0±2.2	0.597	-3.4±1.1	-2.6±1.9	0.505
ΔTOI abdominal (%)	-4.1±3.2	-3.0±2.7	0.070	-5.8±2.6	-1.6±2.7	0.031

pNIV; portable non-invasive ventilation, PLB; pursed lip breathing, ΔHbO_2: change in oxygenated haemoglobin from baseline, ΔHHb: change in deoxygenated haemoglobin from baseline, ΔTOI: change in tissue oxygen index from baseline. Data are presented as mean ± SD