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

3

4        **Chynkiamis N.<sup>1</sup>, Lane ND.<sup>2,4</sup>, Megaritis D.<sup>1</sup>, Manifield J.<sup>1</sup>, Loizou I.<sup>1</sup>, Alexiou C.<sup>1</sup>,**  
5        **Riazati S.<sup>1</sup>, LoMauro A.<sup>3</sup>, Bourke SC.<sup>2,4\*</sup>, Vogiatzis I.<sup>1,2\*</sup>**

6        <sup>1</sup>Department of Sport, Exercise and Rehabilitation, Northumbria University,  
7        Newcastle Upon-Tyne.

8        <sup>2</sup>Northumbria Healthcare NHS Foundation Trust, North Tyneside General Hospital,  
9        Newcastle Upon-Tyne.

10       <sup>3</sup>Dipartimento di Elettronica, Informazione e Bioingegneria, Politecnico di Milano,  
11       Milano, Italy.

12       <sup>4</sup>Translational and Clinical Research Institute, Newcastle University; United Kingdom.

13       \* sharing senior authorship

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

15       **Correspondence:** Dr. Nikolaos Chynkiamis (nikchy@thorax.org.gr) THORAX  
16       Foundation, Research Centre of Intensive Care and Emergency Thoracic Medicine, 3,  
17       Ploutarchou St., 2nd floor 106 75 Athens, Greece

18

**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 $\pm$ SD) (FEV<sub>1</sub>: 55 $\pm$ 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 $\pm$ 0.3 L, p=0.015), inspiratory flow rate (by 0.6 $\pm$ 0.5 L/sec, p=0.049), prolonged expiratory time (by 0.6 $\pm$ 0.5 sec, p=0.006) and duty cycle (by 0.7 $\pm$ 0.6 sec, p=0.007). DH responders showed a reduction in end-expiratory thoracoabdominal DH (by 265 $\pm$ 633 ml) predominantly driven by reduction in the abdominal compartment (by 210 $\pm$ 494 ml); this effectively offset end-inspiratory rib-cage DH. Compared to DH non-responders, DH responders had significantly greater BMI by 8.4 $\pm$ 3.2 kg/m<sup>2</sup>, p=0.022 and tended towards less severe resting hyperinflation by 0.3 $\pm$ 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

60 **New and Noteworthy**

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

## 69 Introduction

70 Expiratory flow limitation (EFL) is an important pathophysiological hallmark in  
71 Chronic Obstructive Pulmonary Disease (COPD), limiting exercise tolerance  
72 secondary to increased dynamic hyperinflation (DH) (13, 38). DH is manifested by  
73 increased end-expiratory lung volume that reduces inspiratory reserve volume (IRV).  
74 This forces COPD patients to breathe close to their total lung capacity (TLC),  
75 increasing both work of breathing and breathlessness (38). Additionally, DH may  
76 cause adverse central hemodynamic effects by reducing venous return, thus  
77 impairing the normal increase in stroke volume and cardiac output during exercise  
78 (1, 50). Non-invasive ventilation (NIV) is one of the ergogenic approaches that has  
79 been implemented to reduce DH and breathlessness, thus improving exercise  
80 tolerance in COPD (3).

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

88 Application of a portable NIV (pNIV) device (VitaBreath, Philips Respironics  
89 Morrisville, PA, USA) was recently shown to increase intermittent exercise tolerance  
90 and improve breathlessness in comparison to the pursed lip breathing (PLB)  
91 technique in 16/24 COPD patients when applied in the first minute of recovery  
92 periods during successive bouts of intermittent exercise (10, 48). VitaBreath is a  
93 portable, handheld, battery-powered, pNIV device that provides an expiratory  
94 positive airway pressure (EPAP) of 8 cmH<sub>2</sub>O and inspiratory positive airway pressure  
95 (IPAP) of 18 cmH<sub>2</sub>O (17). The VitaBreath device is no longer commercially available,  
96 but similar devices may come to market. Nevertheless, the aforementioned studies  
97 (10, 48) provided proof of concept on how NIV can be applied intermittently during  
98 recovery from exercise in patients with COPD, and how to identify patients most  
99 likely to respond to NIV. Furthermore, considering that use of pNIV in activities of  
100 daily living improves anxiety around breathlessness, as well as perceived time of  
101 recovery from it (48), ventilatory support during recovery from exercise is potentially  
102 of value to the COPD patient.

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

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

120 Optoelectronic Plethysmography (OEP) allows breath-by-breath assessment of end-  
121 inspiratory and end-expiratory total and compartmental (rib cage and abdominal)  
122 thoracoabdominal volumes without the necessity to perform IC manoeuvres (2). The  
123 purpose of the present study was to assess total and compartmental  
124 thoracoabdominal volumes during acute application of pNIV during recovery from  
125 exercise. We hoped to better understand why the rate of recovery from DH is slower  
126 with pNIV compared to PLB in DH non-responders compared to DH responders (10,  
127 48).

128 Earlier work has shown that application of continuous positive airway pressure  
129 (CPAP: 7.5-10 cm H<sub>2</sub>O) during exercise is associated with inflation of the rib cage  
130 compartment with concomitant deflation of the abdominal compartment, secondary  
131 to expiratory abdominal muscle recruitment, in the majority of COPD patients (43).  
132 Accordingly, it was reasoned that during acute application of pNIV in recovery from  
133 intermittent exercise, DH responders would exhibit greater recruitment of expiratory  
134 abdominal muscles alongside greater expiratory flow rates when compared to DH  
135 non-responders.

136

## 137 **Methods**

### 138 ***Study design***

139 This was a crossover study investigating the acute effect of pNIV compared to the  
140 PLB technique on thoracoabdominal volumes in recovery from intermittent exercise.  
141 Central hemodynamic responses, local respiratory muscle oxygen availability and  
142 respiratory muscle electromyography activity were also assessed. Patients  
143 underwent two sub-maximal intermittent exercise tests sustained at 80% of peak  
144 work rate (WRpeak) on a cycle ergometer using both pNIV and the PLB technique  
145 during recovery from exercise in a balanced order on the same day. The  
146 investigations were carried out following the rules of the Declaration of Helsinki of  
147 1975 (51), revised in 2013. NHS Research Ethics Committee approval (Ref:  
148 19/NE/0091) and Clinical Trials registration (NCT03848819) were obtained. All  
149 participants provided written informed consent.

### 150 ***Participants***

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

### 157 ***Baseline Assessment – Visit 1***

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

### 165 ***Intermittent Exercise Protocol – Visit 2***

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

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

175 After the termination of the 5<sup>th</sup> exercise bout patients underwent 5 minutes of  
176 measurements during recovery. Patients performed IC manoeuvres to allow  
177 calculation of thoracoabdominal volumes at total lung capacity (TLC) during QB, the  
178 second minute of each exercise bout and each recovery period as previously  
179 described (40). Total and compartmental thoracoabdominal volumes were recorded  
180 by OEP during QB, exercise and recovery periods. Circulatory responses and local  
181 respiratory muscle oxygenation were measured non-invasively using impedance  
182 cardiography technology and near-infrared spectroscopy, respectively throughout  
183 QB, exercise and recovery periods. Electromyography (EMG) activity of respiratory  
184 muscles (intercostal, scalene and rectus abdominis) was recorded during the first  
185 minute of each recovery period using surface electromyography electrodes.  
186 Peripheral oxygen saturation (SpO<sub>2</sub>%) was continuously monitored by a pulse  
187 oximeter (Onyx Vantage 9590, Nonin Medical Inc, USA). Finally, following each  
188 exercise bout dyspnoea and leg discomfort were recorded on the modified 1-10 Borg  
189 scale (6).

#### 190 *pNIV and pursed lip breathing*

191 During the first minute of each recovery period in one of the exercise tests, pNIV was  
192 applied via the VitaBreath device. The VitaBreath is a portable, handheld, battery-  
193 powered, non-invasive ventilation device (pNIV) intended to reduce activity-related  
194 shortness of breath (17). It delivers fixed high inspiratory (18 cm H<sub>2</sub>O) and expiratory  
195 (8 cm H<sub>2</sub>O) pressures, but it can only be used during recovery periods interspersing  
196 bouts of physical activity.

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

#### 202 ***Thoracoabdominal volumes***

203 During both intermittent exercise tests, thoracoabdominal wall kinematics were  
204 assessed by the OEP system (BTS, Milano, Italy) during QB, the second minute of  
205 each exercise bout and throughout the recovery periods as follows: the movement  
206 of 89 retro-reflective markers placed over the anterior, lateral and posterior chest  
207 wall was recorded. Each marker was tracked by eight video cameras (Smart System  
208 BTS, Milan, Italy), four in front of the subject and four behind. Subjects used grasp  
209 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<sup>th</sup> 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<sub>2</sub>), 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 7<sup>th</sup> 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.

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

### 253 ***Statistical analysis***

254 Estimation of sample size within each breathing modality (i.e. pNIV and PLB) was  
255 based on the results of our previous study (48). Using the minimum clinically  
256 important difference in DH assessed by inspiratory capacity manoeuvres defined as  
257 4.5% of predicted resting IC (mean: 120 ml within our previous cohort) and observed  
258 SD: 110 ml (48), an alpha significance level of 0.05 (2-sided) and 80% power, a  
259 minimum total sample size of 13 patients was required. Fourteen patients were  
260 recruited in order to achieve balance in the order that the pNIV and PLB trials were  
261 performed. Seven patients had previously participated in a study undertaken by our  
262 group (48). Data are presented as mean  $\pm$  standard deviation (SD) unless otherwise  
263 stated. DH responders were identified as patients showing a reduction in end-  
264 expiratory thoracoabdominal volume with pNIV at least 120 ml greater than that  
265 seen with PLB at the first minute of recovery, whereas DH non-responders were  
266 those failing to show this degree of response with pNIV compared to PLB (10). The  
267 120 ml dichotomous value was based on our earlier study (10) indicating that  
268 patients showing an reduction in DH  $\geq$  120 ml (40) when using pNIV compared to the  
269 PLB technique were identified as DH responders. Patients showing a decrease in DH  
270  $<$  120 ml, or an increase, in DH using pNIV compared to PLB were defined as DH non-  
271 responders. Independent sample t-tests were employed to compare baseline  
272 characteristics between DH responders and DH non-responders. Two-way repeated  
273 measures ANOVA followed by least significant difference (LSD) post-hoc analysis was  
274 employed to assess differences in total and compartmental thoracoabdominal  
275 volumes, breathing pattern, circulatory responses and local respiratory muscle  
276 oxygenation between both the pNIV device and PLB exercise tests, and between DH  
277 responders and DH-non responders. Activation of respiratory muscle EMG activity is  
278 presented as percentage of change from baseline (QB) and was analysed using  
279 paired sample t-tests. Data present mean values for thoracoabdominal and  
280 compartmental volumes, circulatory responses, local respiratory muscle oxygen  
281 availability, and respiratory muscle EMG activity for: QB, the 5 exercise bouts, the 1<sup>st</sup>  
282 and 2<sup>nd</sup> minutes of all 5 recovery periods as well as the 3<sup>rd</sup>, 4<sup>th</sup> and 5<sup>th</sup> minute of  
283 recovery following the final exercise bout. The level of significance for all analyses  
284 was set at  $p < 0.05$ .

285

## 286    **Results**

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

### 292    ***Thoracoabdominal volumes for all patients***

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

301    With acute pNIV application in the first minute of recovery total end-inspiratory  
302    thoracoabdominal volume was greater compared to PLB application (by:  $230 \pm 207$   
303    ml;  $p=0.047$ ) (Figure 1a), secondary to greater end-inspiratory rib cage volume (by:  
304     $266 \pm 196$ ;  $p=0.005$ ) (Figure 1b). Total end-expiratory thoracoabdominal volumes  
305    were not different ( $p=0.673$ ) between acute PLB and pNIV applications in the first  
306    minute of recovery (Figure 1a). During pNIV application there was a greater increase  
307    in end-expiratory rib cage volume (by  $198 \pm 185$  ml  $p=0.047$  value) (Figure 1b)  
308    compared to PLB, which was partially compensated by the lower end-expiratory  
309    abdominal volume (by  $141 \pm 124$  ml  $p=0.022$ ) (Figure 1c). IRV (relative to TLC at the  
310    end of exercise) was on average  $257 \pm 227$  ( $p=0.038$ ) ml lower with acute pNIV  
311    application compared to PLB, indicating ventilatory constraints (36). At the 5<sup>th</sup>  
312    minute of recovery following the last exercise bout, neither end-inspiratory nor end-  
313    expiratory total thoracoabdominal volumes returned to levels recorded during QB  
314    (Figure 1a).

### 315    ***Thoracoabdominal volumes during exercise***

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

323 responders maintained end-expiratory abdominal volume unchanged from QB in  
324 both trials ( $p>0.05$ ) (Figure 2f). Exercise IRV was not different ( $p=0.391$ ) between DH  
325 responders ( $644\pm513$  ml) and DH non-responders ( $528\pm353$  ml) (Figure 2a & 2d).  
326 During exercise DH responders exhibited greater inspiratory and expiratory flow  
327 rates compared to DH non-responders (Figure 3 a & 3b).

#### 328 ***DH responders in recovery from exercise***

329 Our analysis identified 7 patients as DH responders and 7 patients as DH non-  
330 responders (Table 1). In DH responders, during acute application of pNIV compared  
331 to PLB, total end-expiratory thoracoabdominal volume was lower by  $209\pm422$  ml (38)  
332 (Figure 2a), secondary to significantly lower end-expiratory abdominal volume with  
333 pNIV compared to PLB (by:  $219\pm197$  ml;  $p=0.026$ ) (Figure 2c), thereby indicating  
334 greater expiratory abdominal muscle recruitment. In DH responders during acute  
335 application of pNIV compared to PLB, numerical differences did not reach statistical  
336 significance for total end-inspiratory thoracoabdominal volume (by  $224\pm465$  ml;  
337  $p=0.250$ ) (Figure 2a) consequently to differences in end-inspiratory rib cage volume  
338 (by  $186\pm368$  ml;  $p=0.230$ ) (Figure 2b). IRV with pNIV tended to be lower ( $p=0.078$ )  
339 compared to PLB (by  $302\pm421$  ml) (Figure 2a and Table 2). At the 5<sup>th</sup> minute of  
340 recovery following the last exercise bout, neither end-inspiratory nor end-expiratory  
341 total thoracoabdominal volumes returned to levels recorded during QB (Figure 2a).

#### 342 ***DH non-responders in recovery from exercise***

343 In DH non-responders, during acute application of pNIV compared to PLB, total end-  
344 expiratory thoracoabdominal volume was greater ( $p=0.001$ ) by  $356\pm153$  ml (Figure  
345 2d) secondary to greater end-expiratory rib cage volume with pNIV compared to PLB  
346 (by:  $416\pm86$ ;  $p=0.001$ ) (Figure 2e) and unchanged end-expiratory abdominal volume  
347 (Figure 2f). During acute application of pNIV total end-inspiratory thoracoabdominal  
348 volume was greater compared to PLB (by:  $238\pm218$  ml;  $p=0.047$ ) (Figure 2d),  
349 secondary to greater end-inspiratory rib cage volume (by:  $346\pm199$  ml;  $p=0.004$ )  
350 (Figure 2e). There was no significant difference in IRV between pNIV and PLB  
351 application ( $p=0.252$ ) (Figure 2d and Table 2). At the 5<sup>th</sup> minute of recovery following  
352 the last exercise bout, neither end-inspiratory nor end-expiratory total  
353 thoracoabdominal volumes returned to levels recorded during QB (Figure 2d).

#### 354 ***Differences between DH responders and non-responders in recovery from exercise***

355 Considering pNIV application alone, DH responders compared to DH non-responders  
356 exhibited a reduction in end-expiratory thoracoabdominal DH (by  $265\pm633$  ml)  
357 predominantly driven by reduction in the abdominal compartment ( $210\pm494$  ml),  
358 thereby effectively offsetting end-inspiratory rib cage DH.

359

### 360 ***Breathing pattern in DH responders and DH non-responders***

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

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

### 383 ***Differences in breathing pattern between DH responders and DH non-responders***

384 When pNIV was applied, DH responders compared to DH non-responders exhibited  
385 greater tidal volume (by  $0.8 \pm 0.5$  L,  $p = 0.015$ ), inspiratory flow rate (by  $0.6 \pm 0.5$  L/sec,  
386  $p = 0.049$ ), prolonged expiratory time (by  $0.6 \pm 0.5$  sec,  $p = 0.006$ ) and duty cycle (by  
387  $0.7 \pm 0.6$  sec,  $p = 0.007$ ) whilst breathing frequency was lower ( $p = 0.019$ ) (Table 2).

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

### 393 ***Central haemodynamic responses***

394 CO was unaffected by acute pNIV application compared to PLB in both DH  
395 responders and DH non-responders (Figure 4c & 4f). However, in DH responders,  
396 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 5<sup>th</sup> 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 5<sup>th</sup> 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:  $20\pm16\%$ ;  $p=0.043$ ), scalene (by:  $50\pm33\%$ ;  $p=0.013$ ) and rectus abdominis (by:  $67\pm57\%$ ;  $p=0.014$ ) 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:  $32\pm22\%$ ;  $p=0.009$ ) and scalene (by:  $32\pm30\%$ ;  $p=0.047$ ) muscles and greater EMG activity of rectus abdominis muscle (by:  $33\pm31\%$ ;  $p=0.049$ ) (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:  $2.3\pm2.1$   $\mu\text{mol/L}$ ;  $p=0.048$ ) and rectus abdominis muscle (by:  $1.8\pm1.7$   $\mu\text{mol/L}$ ;  $p=0.047$ ). In DH non-responders, pNIV application compared to PLB caused greater levels of deoxygenated haemoglobin in intercostal (by:  $2.1\pm1.5$   $\mu\text{mol/L}$ ;  $p=0.040$ ) and rectus abdominis (by:  $4.6\pm4.0$   $\mu\text{mol/L}$ ;  $p=0.045$ ) muscles. There were no differences in the pattern and magnitude of response of deoxygenated haemoglobin of intercostal and abdominal muscles between DH responders and DH non-responders.

## 432 **Discussion**

### 433 ***Main findings***

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

### 445 ***Study novelties***

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

### 458 ***Differences in baseline characteristics between DH responders and non-responders***

459 One significant difference between DH responders and DH non-responders was  
460 elevated BMI presented in the group of DH responders. A recent study (10) argued  
461 that a possible mechanism that allowed DH responders compared to DH non-  
462 responders to benefit from pNIV was the increased BMI (10). It has previously been  
463 reported that the respiratory muscles of COPD with high BMI might have a  
464 mechanical advantage in comparison to patients with normal BMI (35). This has been  
465 attributed to the increased inspiratory capacity (i.e. lower resting hyperinflation) in  
466 patients with high BMI, which was evident in the DH responders in the present  
467 study. Moreover, patients with high BMI might have an advantage when using pNIV,  
468 which applies a high expiratory positive airway pressure (8 cmH<sub>2</sub>O) in comparison to  
469 other NIV devices (7, 19, 22, 44, 45, 47). It is known that intrinsic positive end-

470 expiratory pressure (PEEPi) needs to be closely matched with extrinsic positive end-  
471 expiratory pressure (PEEPe) (31). If PEEPe is significantly lower than PEEPi there will  
472 be no improvement in operational lung volumes (14, 32). In contrast, if PEEPe is  
473 much greater than PEEPi, dynamic hyperinflation will worsen and result in adverse  
474 central haemodynamic responses (16, 28). Patients with higher BMI exhibit greater  
475 PEEPi (35), thus NIV devices with higher expiratory positive airway pressure (PEEPe),  
476 such as the VitaBreath device in the present study (8 cm H<sub>2</sub>O), might be better suited  
477 to patients with high BMI (10). Future devices may be able to tailor the expiratory  
478 pressure to overcome expiratory flow limitation in individual patients.

#### 479 ***DH responders***

480 Application of pNIV compared to PLB was associated with increased end-inspiratory  
481 rib cage and total thoracoabdominal volumes in DH responders. This finding is  
482 explained by the high fixed IPAP (18 cmH<sub>2</sub>O) provided by the VitaBreath device, but  
483 is in line with other NIV methods showing an inflation of the rib cage compartment  
484 with NIV application (43). However, application of pNIV compared to PLB lessened  
485 end-expiratory abdominal and total thoracoabdominal volumes in DH responders.

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

505 DH responders were less flow limited during exercise and during acute pNIV  
506 application compared to DH non-responders, inferred by the greater inspiratory and  
507 expiratory flow rates (Figure 3), allowing them to increase tidal volume more than  
508 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).

540

#### 541 ***DH non-responders***

542 Application of pNIV compared to PLB was associated with increased end-inspiratory  
543 and end-expiratory rib cage volumes. However, the increase in end-expiratory rib  
544 cage volume was not compensated by a reduction in end-expiratory abdominal  
545 volume as reported above for DH responders. This led to an increase in total end-  
546 expiratory thoracoabdominal volume and thus DH, which limited tidal volume  
547 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<sub>2</sub>O) 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

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

### 589 ***Haemodynamic responses***

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

### 595 ***Study limitations***

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

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

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

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

### 632 ***Clinical implications***

633 The delayed recovery of dynamic hyperinflation following cessation of intermittent  
634 exercise has important clinical implications when designing rehabilitative exercise  
635 training regimes for patients with severe COPD, particularly if NIV is to be applied  
636 only during recovery from exercise. It is apparent from our results that whilst acute  
637 pNIV application was effective only in a specific subgroup of patients, clinical  
638 characteristics such as baseline hyperinflation can help predict response.  
639 Furthermore, COPD patients whose breathing control resembles that of a healthy  
640 individual in recruiting expiratory muscles during exercise (1, 50) are more likely to  
641 benefit from NIV; they may mitigate rib cage dynamic hyperinflation by expiratory  
642 abdominal muscle recruitment. Nevertheless, DH non-responders were less  
643 breathless and had greater expiratory flow with pNIV, therefore pNIV was not  
644 without some benefit even to this subgroup of patients. During recovery from  
645 exercise the improvement in DH lasted only transiently (1-min, during pNIV  
646 application) in DH responders. If implementing the use of NIV in the pulmonary  
647 rehabilitation setting NIV should perhaps be applied for longer to facilitate complete  
648 recovery of DH before moving to a new exercise task. However, considering the  
649 variation in response we have reported, it is important that clinicians assess the  
650 response to pNIV on an individual basis in order to verify whether using a portable  
651 NIV device during rehabilitation or at home makes the patient feeling better or  
652 worse. An earlier study from our group showed that in DH responders, use of pNIV  
653 during daily activities over a 12-week period made them less anxious about  
654 becoming breathlessness compared to DH non-responders (10).

655

### 656 ***Conclusions***

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

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663

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668

669    **Disclosure**

670    The authors declare that they have no competing interests.

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## Figures legends

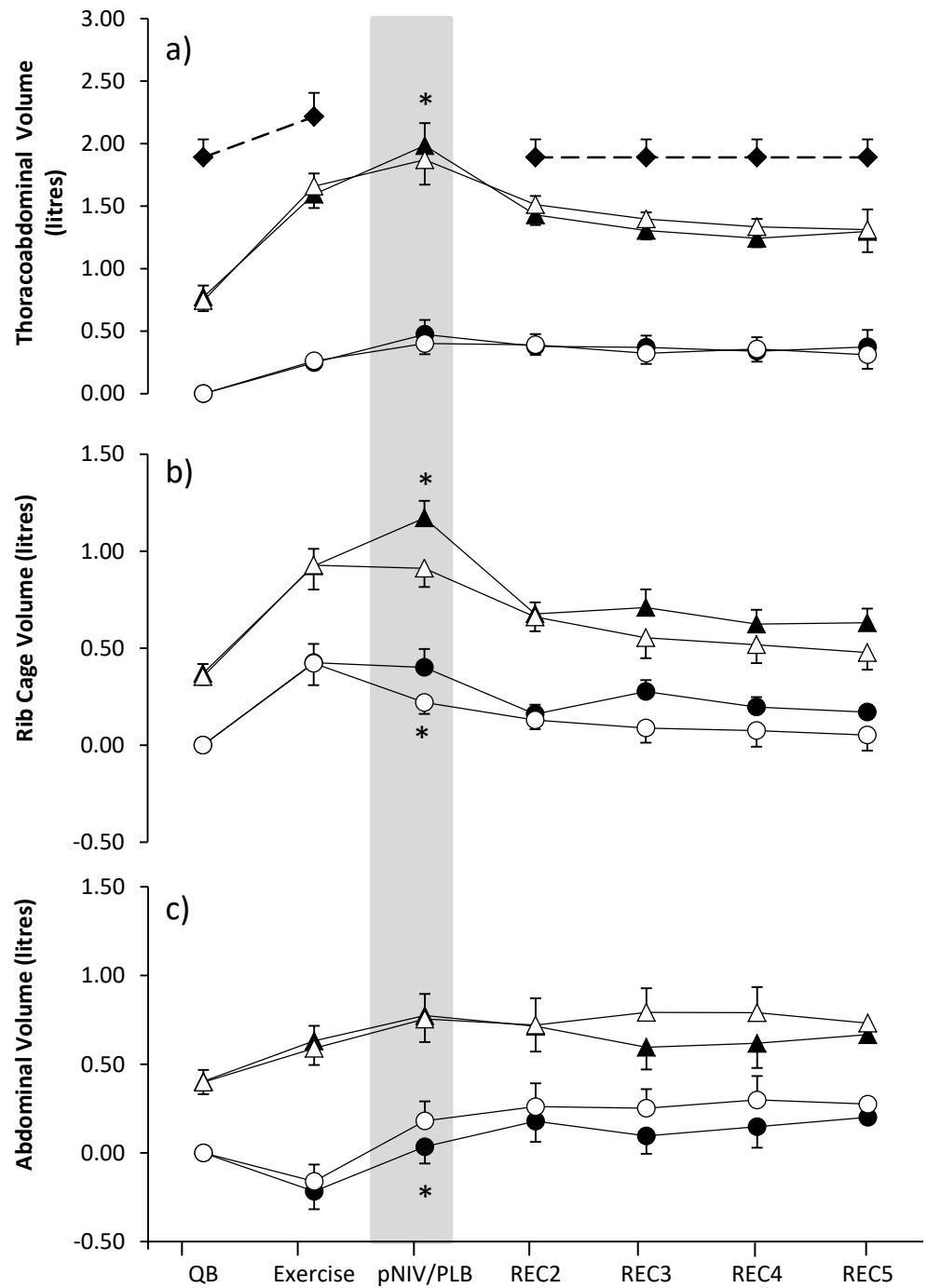
**Figure 1.** Effect of the application of portable non-invasive ventilation (pNIV) (closed symbols) compared to pursed lip breathing (PLB) (open symbols) on: a) total thoracoabdominal volume, b) rib cage volume and c) abdominal volume in all patients. Circles: end-expiratory volume, triangles: end-inspiratory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

Figure 1



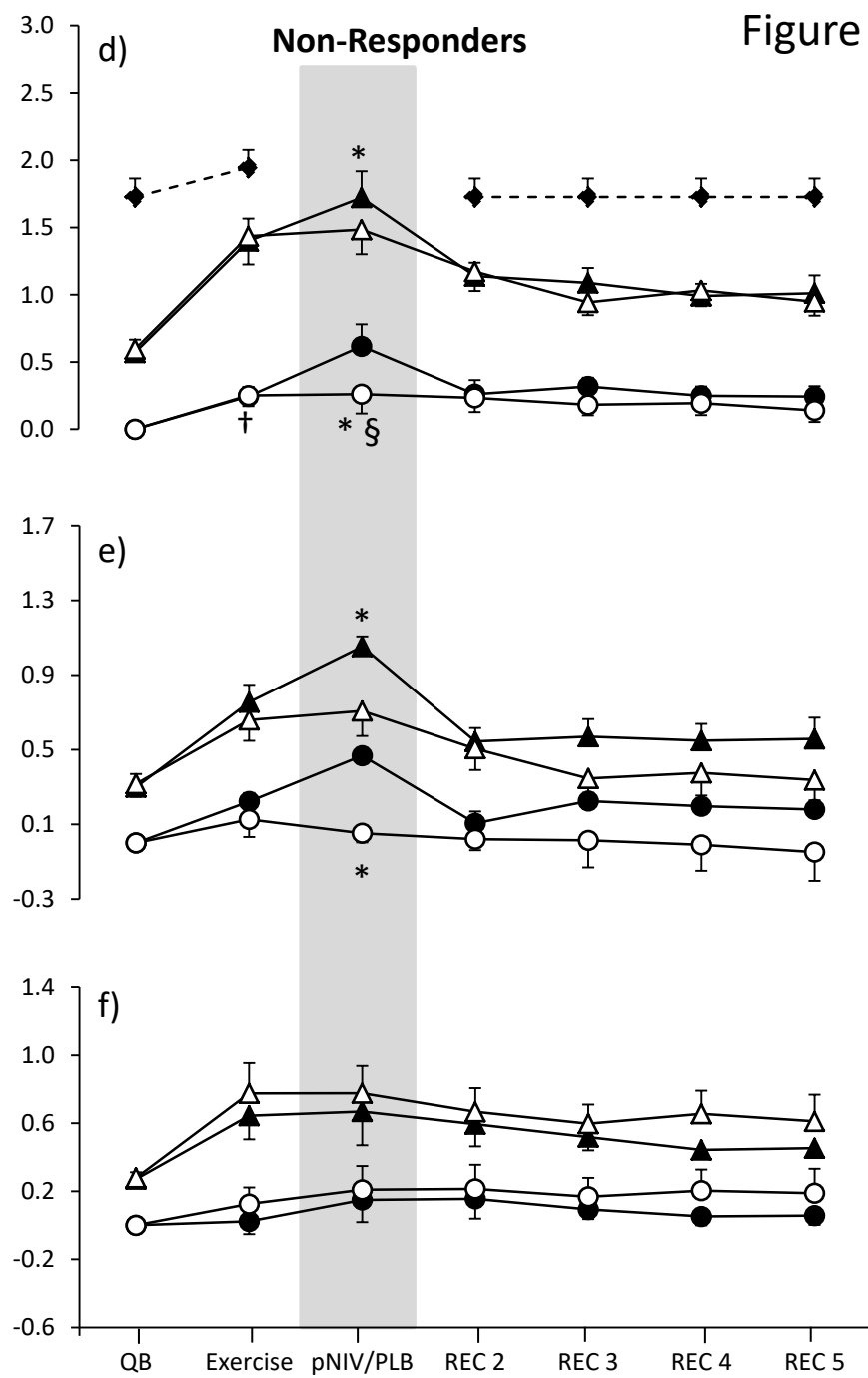
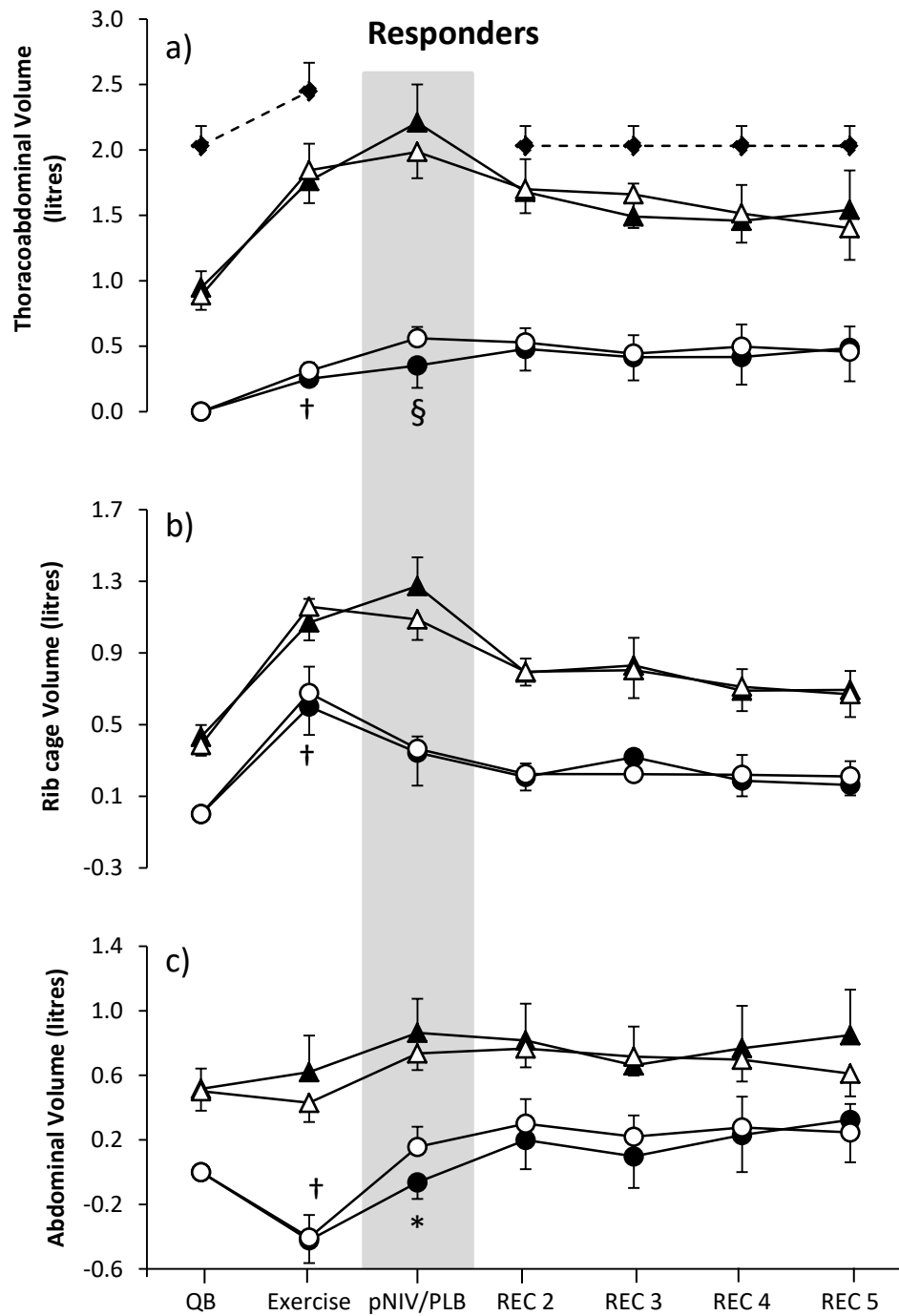
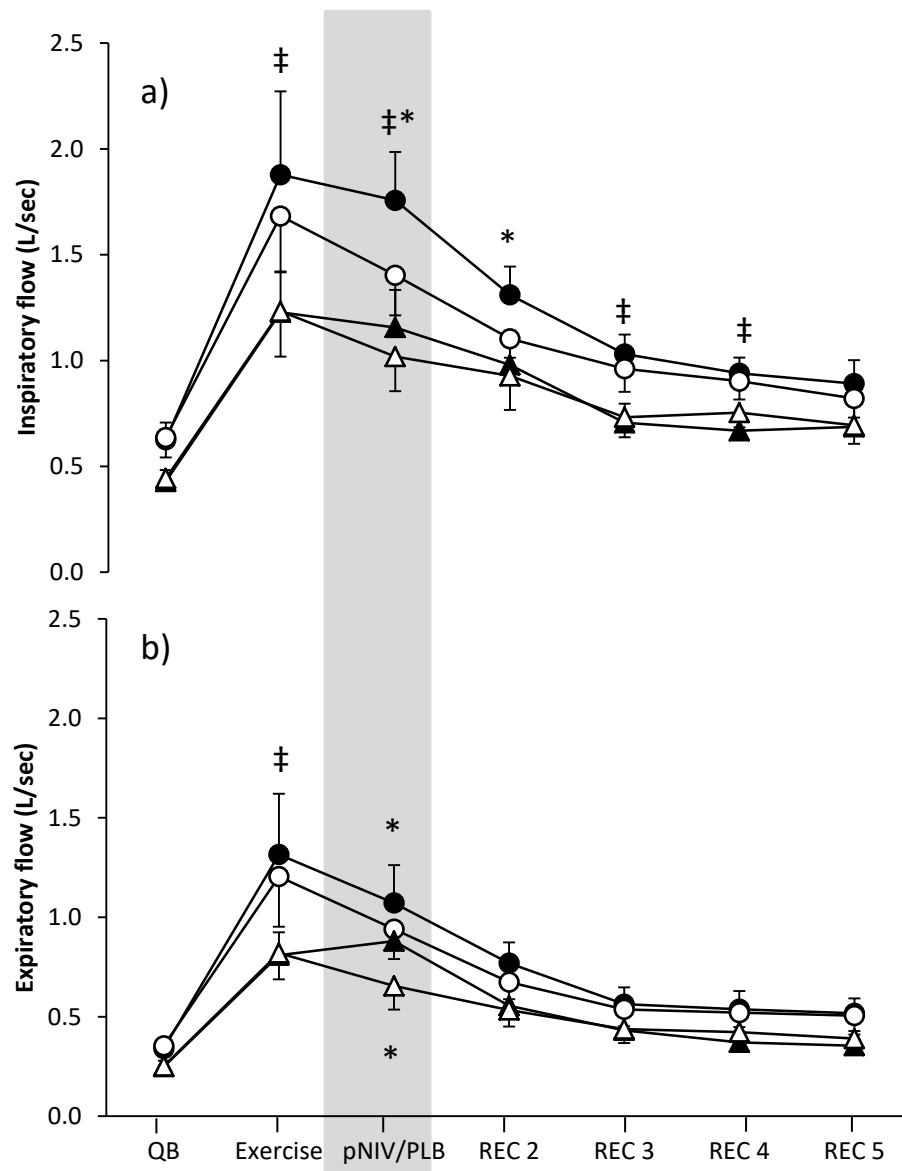
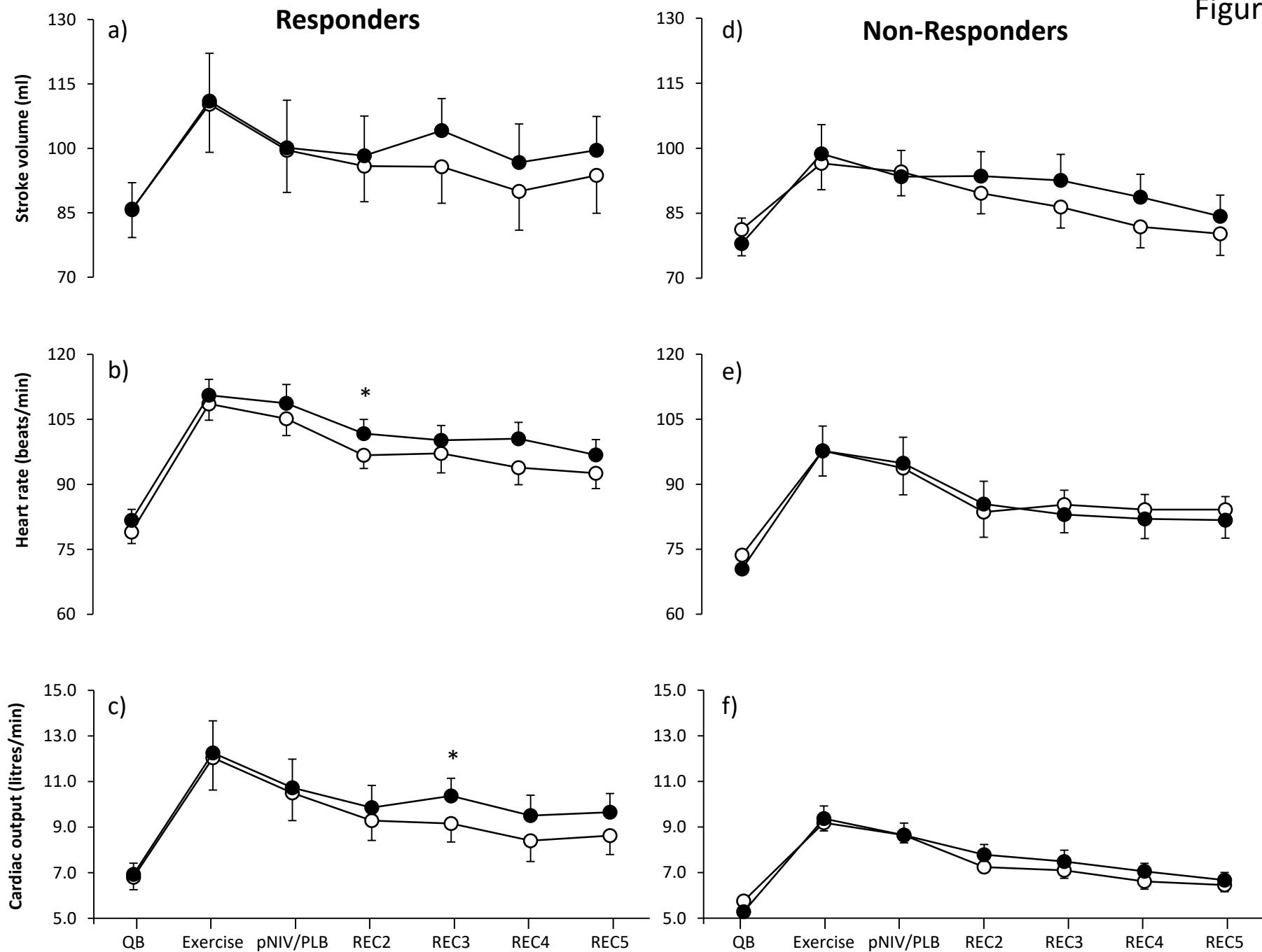


Figure 3





**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 <sup>2</sup> )	28.6±7.2	32.8±6.7	24.4±5.0	0.022
FEV <sub>1</sub> (L)	1.34±0.69	1.53±0.81	1.14±0.53	0.301
FEV <sub>1</sub> (% 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 <sub>1</sub> /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 <sub>2</sub> peak (% 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<sub>1</sub>, 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<sub>2</sub>peak, 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
<b>V<sub>T</sub> (L)</b>	1.9±0.7	1.4±0.5	0.002	1.1±0.3*	1.2±0.4	0.369
<b>bf (breaths/min)</b>	21±3	22±5	0.478	27±5*	20±4	0.002
<b>V<sub>E</sub> (L/min)</b>	39.0±16.6	32.5±12.4	0.009	29.1±7.6	23.4±9.2	0.018
<b>Ti (sec)</b>	1.1±0.2	1.2±0.3	0.454	1.0±0.2	1.3±0.3	0.019
<b>Te (sec)</b>	1.9±0.4	1.8±0.3	0.765	1.3±0.3*	2.1±0.6	0.001
<b>Ttot (sec)</b>	3.0±0.4	3.0±0.5	0.828	2.3±0.4*	3.4±0.8	0.001
<b>Inspiratory flow rate (L/sec)</b>	1.8±0.6	1.4±0.5	0.001	1.2±0.4*	1.0±0.4	0.064
<b>Expiratory flow rate (L/sec)</b>	1.1±0.5	0.9±0.4	0.048	0.9±0.2	0.7±0.3	0.011
<b>IRV (ml)</b>	200±446	502±477	0.078	240±549	444±246	0.252
<b>Dyspnoea (Borg)</b>	3.1±1.3	3.0±1.3	0.745	2.5±0.7	3.6±1.1	0.001
<b>Leg Discomfort (Borg)</b>	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<sub>T</sub>: tidal volume, bf: breathing frequency, V<sub>E</sub>: 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
<b>Intercostal (% baseline)</b>	111±26	91±28	0.043	103±33	135±70	0.009
<b>Scalene (% baseline)</b>	192±81	142±38	0.013	143±43	175±79	0.047
<b>Rectus abdominis (% baseline)</b>	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
<b>ΔHbO<sub>2</sub> intercostal (μmol/L)</b>	-2.0±4.2	-3.4±3.0	0.120	-1.7±1.6	-2.4±2.1	0.449
<b>ΔHbO<sub>2</sub> abdominal (μmol/L)</b>	0.8±1.0	-0.2±1.5	0.421	0.8±6.2	-3.3±3.9	0.378
<b>ΔHHb intercostal (μmol/L)</b>	3.5±3.0	1.2±1.4	0.048	5.3±3.7	3.2±4.7	0.040
<b>ΔHHb abdominal (μmol/L)</b>	4.6±1.7	2.8±3.8	0.047	3.5±3.3	-1.1±1.8	0.045
<b>ΔTOI intercostal (%)</b>	-3.0±1.9	-4.0±2.2	0.597	-3.4±1.1	-2.6±1.9	0.505
<b>ΔTOI abdominal (%)</b>	-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<sub>2</sub>: 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