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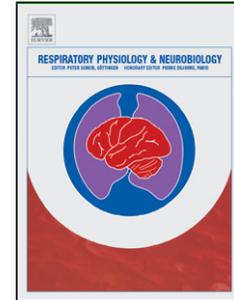
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Hemodynamic effects of portable non-invasive ventilation in healthy men

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Highlights

- Short application of portable NIV does not cause adverse haemodynamic effects in healthy individuals

- Portable NIV makes the respiratory muscles work harder in healthy individuals.
- Caution should be taken to avoid worsening of dyspnoea induced by pNIV in patients with acute respiratory failure.

Abstract

VitaBreath is a portable, non-invasive ventilation device (pNIV) that relieves shortness of breath in COPD by delivering fixed inspiratory and expiratory positive airway pressures (IPAP/EPAP: 18/8 cmH_2O). Fixed pressures may cause circulatory compromise. We investigated the circulatory effects of pNIV during normal breathing (NB) and after Eucapnic Voluntary Hyperpnoea trials (EVH) sustained at 80% MVV. In a balanced order sequence, 10 healthy men performed four trials on one visit: 1-min of pNIV (intervention) or 1-min quiet breathing (QB) during NB; and 1-min pNIV (intervention) or 1-min QB during recovery from 3-min EVH. Compared to QB, pNIV application was associated with greater cardiac output (CO: 1.6 ±1.9 $L.min^{-1}$; P=0.03). One minute into recovery from EVH, pNIV caused greater CO (2.2 ±1.6 $L.min^{-1}$; P=0.01) compared to QB. Mean blood pressure was not different with pNIV compared to control. pNIV increased thoracoabdominal volumes and breathing frequency during NB and recovery from EVH. pNIV application does not induce adverse hemodynamic effects in healthy men.

160 words

1. Introduction

Non-invasive ventilation (NIV) is commonly used in clinical practice in people with respiratory disorders to aid ventilation by reducing the work of breathing (WoB). This is achieved by manipulating pressure gradients within a facemask or other interface to facilitate air transfer and maintain airway patency. Application of NIV during exercise appears to elicit clinically meaningful improvements in exercise tolerance in patients with chronic obstructive pulmonary disease (COPD) (by 165±88 sec) [Menadue, et al. 2014,Puente-Maestu, et al. 2016] and chronic heart failure (by 88±27 sec) (CHF) [Bundchen, et al. 2014]. Traditional NIV is, however, cumbersome to use during exercise training or activities of daily life [Ambrosino and Cigni 2015,Ambrosino and Xie 2017].

The VitaBreath is a new intermittent bi-level positive airway pressure support device providing portable NIV (pNIV) that administrates fixed positive airway pressures both during inspiration (18 cmH2O) and expiration (8 cmH2O) for short periods of time [Hardy and Jasko 2015]. It was designed to relieve breathlessness during daily physical activities [Hardy and Jasko 2015]. However, it can only be used in recovery either during intermittent exercise or habitual activities of daily living [Hardy and Jasko 2015].

Recently, COPD patients using the VitaBreath device had lower perceived anxiety levels and perceived a faster recovery time from breathlessness during habitual physical activities [Vogiatzis, et al. 2019]. Application of pNIV, during the rest periods of an intermittent exercise protocol, reduced dynamic hyperinflation (DH) and breathlessness and increased exercise tolerance compared to the pursed lip breathing (PLB) technique [Vogiatzis, et al. 2019]. Interestingly, in the majority of patients, stroke volume (SV) and cardiac output (CO) were increased during successive exercise bouts when pNIV was used compared to the PLB [Vogiatzis, et al. 2019]. This finding suggests that intermittent application of the VitaBreath device during recovery from exercise does not adversely influence central haemodynamic responses. This is contrary to the effects of other continuous NIV devices on central haemodynamic responses in healthy and diseased groups [Ambrosino, et al. 1993,Baratz, et al. 1992,Diaz, et al. 1997,Montner, et al. 1994,Naughton, et al. 1995,Philip-Joet, et al. 1999,Valipour, et al. 2005]. The increase in CO with the VitaBreath compared to PLB was attributed to improved venous return secondary to a reduction in DH and associated large intrathoracic pressure swings [Vogiatzis et al. 2019].

In healthy participants not experiencing DH, application of continuous or bi-level IPAP and EPAP at rest [Montner, et al. 1994,Philip-Joet, et al. 1999,Valipour, et al. 2005] and at high levels of respiration [Stark-Leyva, et al. 2004], have had varied results either causing reductions in SV and CO, secondary to increased intrathoracic pressures [Grubler, et al. 2017,Mahmood and Pinsky 2018] or no significant circulatory effects [Leech and Ascah 1991]. These different results may, in part, be due to different devices and study protocols applied. The influence of intermittent bi-level fixed positive airway pressure support has not previously been studied in healthy participants. The aim of this study was, therefore, to investigate the

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effect of intermittent use of pNIV on central haemodynamic regulation in the absence of confounding factors due to disease, at rest and following isocapnic hyperpnoea trials sustained at levels of ventilation exhibited during vigorous exercise. The rationale for using isocapnic hyperpnoea trials rather than exercise was to remove competition for blood flow between the respiratory and locomotor muscles as a confounding variable [Sheel, et al. 2018]. We hypothesised that compared to quiet breathing, the short period of acute (1-min) application of fixed IPAP and EPAP with pNIV, would not cause a reduction on central hemodynamic responses in healthy men at rest or following the hyperpnoea trials.

2. Methods

2.1 Participants

Ten healthy males aged 18 to 35 years participated in the study (Table 1). Current smokers and people with asthma were excluded from the study. This study was approved by Northumbria University Ethics Committee (No: 7936) and written informed consent was provided by all participants prior their participation.

Table 1. Subject baseline data

Variable	n=10
Age (years)	24.9±4.2
Height (meters)	1.82±0.07
Weight (kg)	84.3±14.3
BMI	25.4±3.6
FEV_1 (L)	3.89±0.34
FEV_1 % predicted	92±3
FVC (L)	5.39±0.50
FVC % predicted	98±3
CO (L.min^{-1})	6.2±1.1
SV (ml)	88.5±16.4
HR (beats.min^{-1})	71±9
SBP (mmHg)	127±18
DBP (mmHg)	79±8
MBP (mmHg)	95±12

Data are presented as mean±SD; BMI, body mass index; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; CO, cardiac output; SV, stroke volume; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure

2.2 Study design

This was an interventional repeated measures crossover design study. The acute effect of the application of the VitaBreath device compared to quiet breathing (QB) was assessed separately during two different breathing trials, namely normal breathing (NB) and Eucapnic Voluntary Hyperpnoea (EVH). In a balanced order sequence within each breathing trial, subjects performed two trials on one visit: i) 1-min of pNIV (intervention) or 1-min QB (control) during NB; and ii) 1-min pNIV (intervention) or 1-min QB (control) during recovery from the 3-

min EVH trial (Figure 1). Within each breathing modality (NB or EVH) participants rested for 10 minutes between trials.

2.3 Participants' preparation

Upon arrival to the laboratory and prior any intervention, participants were familiarised with the use of the VitaBreath device for 15 min. Afterwards they performed a spirometry test in order to obtain FEV_1 and calculate maximal voluntary ventilation (MVV), using the following formula: MVV= FEV_1 x 37.5 [Wasserman, et al. 1994]. Then, following skin preparation markers for Opto-Electronic Plethysmography (OEP, BTS, Italy) and pads for the physio-flow device (Enduro, PF-07, Manatec Biomedical, France) were attached to the chest wall.

2.4 Central Haemodynamic measurements

During all trials, participants were connected to a portable cardiographic conduction device using impedance cardiography (Physio Flow). The validity of CO recordings using Physio Flow in comparison to the dye dilution method and the direct Fick method has been certified in healthy people and patients [Charloux, et al. 2000,Louvaris, et al. 2019,Tan, et al. 2006]. Cardiac output (CO), heart rate (HR) and stroke volume (SV) were recorded continuously at 6s intervals as previously detailed [Nasis, et al. 2015]. Six electrodes were placed in all subjects, 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)] [Nasis, et al. 2015].

2.5 Blood pressure, ventilatory and gas exchange measurements

During all trials, blood pressure was measured continuously using a finger cuff (Finapres, Med Systems M2 Finometer Midi, Enscheda, Netherlands). In addition, tidal volume, breathing frequency, minute ventilation and gas exchange variables were measured continuously during normal breathing and EVH trials using a gas exchange analyser (Cortex, METALYZER® 3B, Leipzig, Germany) but not during pNIV application.

2.6 Operational thoracoabdominal volume measurements

During all trials, chest wall kinematics were measured by the OEP (BTS, Milano, Italy) as follows: the movement of 89 retro-reflective markers placed front and back over the chest wall from clavicles to pubis 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 were grasp handles positioned at the mid sternum level which lifted the arms away from the rib cage so that lateral markers can be visualised. Dedicated software reconstructs the three-dimensional coordinates of the markers in real time by stereophotogrametry and calculates total and compartmental chest wall volume and volume variations using Gauss's theorem. The chest wall was modelled as being composed of three compartments—the pulmonary and abdominal rib cage (V_{rcp} and V_{rca}), and the abdomen (V_{ab}). Total thoracoabdominal volume (V_{cw}) is the sum of the three compartmental volumes.

2.7 Normal Breathing in ambient air trials

Participants undertook two seated normal breathing trials either breathing quietly (QB) throughout for seven minutes (control) or breathing quietly (QB) for the first 3 minutes followed by one minute breathing via the VitaBreath device (pNIV), followed by QB for the remaining 3 minutes (intervention) (Figure 1a).

2.8 Eucapnic Voluntary Hyperpnoea Trials (EVH)

The protocol for the seated resting EVH trials was as follows: after two minutes of QB participants were asked to increase their ventilation rate to 80% of their MVV and maintain this targeted ventilation rate for three minutes. Experimenters provided verbal guidance to instruct the participants to adjust the rate and depth of their breathing such that the target ventilation was obtained and held constant to within 5%. During the EVH trials all participants breathed from a gas reservoir Douglas bag containing 5% CO_2, 21% O_2, and 74% N_2 to maintain arterial CO_2 [Vogiatzis, et al. 2010]. After three minutes of breathing at the target ventilation rate participants either breathed room air quietly (QB) for three minutes (control) or breathed through the VitaBreath device for one minute (pNIV) followed by 2 minutes of QB in room air (intervention) (Figure 1b).

2.9 Sample size estimation

Verification of sample size was based on the study of Philip-Joet and colleagues [Philip-Joet, et al. 1999] comparing 10-min application of bi-level positive airway pressure (BiPAP) to control breathing at rest. Based on the mean difference in stroke volume of 10 ml between BiPAP and control breathing, and a standard deviation (SD) of 8 ml, an alpha significance level of 0.05 (2-sided) and 80% power, a minimum total sample size of 10 participants was calculated to be sufficient to detect significant differences in stroke volume between pNIV and control breathing trials.

2.10 Statistical analysis

Data are presented as mean (95% Confidence Interval (CI)) unless otherwise stated. Visual inspection of histograms and Q-Q plots was used to check whether data were normally distributed at baseline. During the normal breathing trials paired sample t-tests were employed to investigate the primary outcome measure; the acute effect of 1-min pNIV application on central hemodynamic and breathing pattern variables in comparison to control breathing. Secondary outcome measures were assessed using two-way ANOVA with repeated measurements across the different time points. Where significance was reached, LSD corrected post-hoc analysis was used to compare central hemodynamic and thoracoabdominal volume responses during the EVH trials (with and without application of pNIV) across different time points. The level of significance for all analyses was set at $p < 0.05$.

3. Results

3.1 Central Haemodynamic effects during NB trials

Compared to QB, 1-min application of pNIV increased SV [by 8.7 (0.7-16.7) ml (p=0.037)], HR [by 10 (3-16) beats.min^{-1} (p=0.008)] and CO [by 1.6 (0.2-3.0) L.min^{-1} (p=0.028)] (Table 2). There were no differences in systolic, diastolic or mean blood pressure when pNIV was applied compared to QB (Table 2).

Table 2. Acute effect of 1-min pNIV application during NB on central haemodynamics

	Normal Breathing		
	QB	pNIV	p
SV (ml)	87.4±16.2	96.1±24.2	0.037
HR (beats.min^{-1})	72±8	82±14	0.008
CO (L.min^{-1})	6.4±1.1	8.0±2.9	0.028
SBP (mmHg)	126±20	122±14	0.113
DBP (mmHg)	77±13	77±11	0.840
MBP (mmHg)	94±14	91±11	0.067

Data are presented as mean±SD; QB, quiet breathing; pNIV, portable non-invasive ventilation; SV, stroke volume; HR, heart rate; CO, cardiac output; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure;

3.2 Central Haemodynamic effects during EVH trials

Stroke volume was greater with the application of pNIV compared to QB (p=0.005) (Figure 2a). During both EVH trials SV increased from baseline [pNIV: by 8.1 (1.0-15.1) ml (p=0.030); QB: by 6.8 (1.6-11.9) ml (p=0.015)]. There were no differences between the trials (p=0.308). During application of pNIV, SV was greater compared to QB [by 13.3 (5.1-12.5) ml (p=0.005)] (Figure 2a). In the 1st min into recovery from pNIV application, SV remained elevated compared to QB [by 6.6 (2.3-11.0) ml (p=0.007)] and returned to baseline on the 2nd min of recovery following pNIV application (Figure 2a).

Heart rate was greater with the application of pNIV compared to QB (p=0.001) (Figure 2c). HR increased from baseline in both EVH trials [pNIV: by 16 (11-20) beats·min^{-1} (p=0.001); QB: by 15 (12-19) beats·min^{-1} (p=0.001)]. There were no differences between the trials (p=0.151). HR was greater compared to QB when pNIV was applied [by 10 (5-16) beats·min^{-1}] (p=0.002) (Figure 2c). In the 1st min into recovery following pNIV application, HR remained elevated [by 9 (5-14) beats·min^{-1}] in comparison to QB (p=0.002) and returned to baseline on the 2nd min of recovery following pNIV application (Figure 2c).

CO was greater with the application of pNIV compared to QB breathing (p=0.001) (Figure 2e). CO increased from baseline when EVH was applied in both pNIV [by 2.2(1.4-2.9) L.min^{-1} (p=0.001)] and QB trials [by 1.9 (1.4-2.5) L.min^{-1} (p=0.001)] (Figure 2e). There were no differences between the trials (p=0.060). However, when participants used pNIV following EVH, CO was greater compared to QB [by 2.1 (1.0-3.3) L.min^{-1}] (p=0.002). CO remained elevated during the 1st min of recovery following application of pNIV [by 1.4 (0.8-2.0) L.min^{-1}

(p=0.001)] compared to QB and returned to baseline on the 2nd min of recovery following pNIV application (Figure 2e). During the EVH trials and in recovery from these trials, there were no differences in systolic, diastolic or mean blood pressure (p=0.393; p=0.092, p=0.148, respectively), with the application of pNIV compared to QB (Figure 2).

3.3 Thoracoabdominal volumes

A typical example of absolute thoracoabdominal volume measurements obtained during the normal breathing (A) and EVH trials (B) is shown in figure 3. During both normal breathing and EVH trials pNIV application was associated with increased total chest wall tidal volumes taking place via an increase in both end-expiratory and end-inspiratory total chest volumes. In contrast, during EVH the increase in total chest wall tidal volume was accomplished by a decrease in end-expiratory and an increase in end-inspiratory chest wall volumes (Figure 3).

Compared to QB, 1-min of pNIV application induced greater total end-expiratory [by 0.7 (0.2-1.1) L (p=0.008)] and greater total end-inspiratory [by 1.4 (1.0-1.8) L p<0.001] chest wall volumes during the normal breathing trials (Table 3).

During the EVH trials, pNIV application was associated with greater end-expiratory (p=0.005) and end-inspiratory (p=0.001) chest wall volumes compared to QB. Specifically, during the 3-min EVH period total end-expiratory volume was decreased from baseline [pNIV: by 0.5 (0.2-0.7) L (p=0.003); QB: by 0.4 (0.1-0.7) L (p=0.022)]; whereas total end-inspiratory volume was increased from baseline [pNIV: by 0.5 (0.1-0.9) L (p=0.032); QB: by 0.6 (0.1-1.2) L (p=0.027)]; (Figure 4a). There were no significant differences in end-expiratory or end-inspiratory volume between the trials [(p=0.596) and (p=0.706), respectively].

One minute into recovery following EVH, pNIV application was associated with greater total end-expiratory volume [by 0.5 (0.3-0.8) L (p=0.001)] compared to QB (Figure 4a and Table 3); this was achieved by greater changes in all end-inspiratory compartmental volumes, namely the rib cage pulmonary [by 0.2 (-0.1-0.5) L (p=0.141)] (Figure 4b), the rib cage abdominal [by 0.3 (-0.1-0.5) L (p=0.002)] (Figure 4c) and the abdominal compartment [by 0.1 (-0.1-0.3) L (p=0.433)] (Figure 4d).

Compared to QB, pNIV administration one minute into recovery following EVH was associated with greater total end-inspiratory volume [by 1.1 (0.8-1.4) L (p=<0.001)] (Figure 4a and Table 3)) and greater compartmental volumes, namely the rib cage pulmonary [by 0.4 (0.1-0.8) L (p=0.024)] (Figure 4b), the rib cage abdominal [by 0.4 (0.3-0.6) L (p=0.001)] (Figure 4c) and the abdominal compartment [by 0.2 (-0.1-0.5) L (p=0.107)] (Figure 4d).

During the normal breathing trials, application of pNIV compared to QB decreased fractional contributions of the abdominal wall volume (p=0.015) (Figure 5a). Compared to QB during recovery from EVH, pNIV application was associated with increased fractional contribution of the rib cage abdominal volume (p=0.019) and decreased (p=0.030) fractional contribution of the abdominal wall volume (Figure 5b).

3.4 Breathing pattern

Table 3 shows breathing pattern variables with the use of the VitaBreath device compared to QB, during the normal breathing and EVH trials. Compared to QB, application of pNIV during normal breathing and EVH trials reduced inspiratory and expiratory time resulting in a reduction in total breathing cycle time (NB: p=0.018 and EVH p=0.026). In addition, application of pNIV compared to QB during the normal breathing and EVH trials, induced greater minute ventilation secondary to increased tidal volume and breathing frequency. Hyperventilation

was associated with a reduction in end-tidal CO_2 recorded during the first minute of recovery (Table 3). Compared to QB there was an increase in the index of shortening velocity of the rib cage inspiratory muscles (NB: p=0.003 and EVH p=0.001), the inspiratory abdominal muscles (diaphragm) (NB: p=0.011 and EVH p=0.001) and the expiratory abdominal muscles when pNIV was applied (NB: p=0.060 and EVH p=0.015) (Table 3). The use of the device was well tolerated by all subjects.

Table 3. Effect of 1-min pNIV application during the normal breathing trials and during the 1st min following EVH on respiratory variables

	Normal Breathing		EVH	
	QB	pNIV	QB	pNIV
Total end-expiratory chest wall volume (L)	0.0±0.1	0.7±0.7*	0.0±0.3	0.5±0.4*
Total end-inspiratory chest wall volume (L)	1.1±0.4	2.5±0.8*	1.5±0.5	2.6±0.5*
Inspiratory time (s)	2.0±0.5	1.3±0.2*	1.7±0.6	1.1±0.3*
Expiratory time (s)	2.5±0.8	1.7±0.7*	1.9±0.6	1.3±0.5
Total breathing cycle time (s)	4.5±1.2	3.0±0.7*	3.6±1.1	2.5±0.8*
Tidal volume (L)	1.0±0.2	1.7±0.6*	1.6±0.5	2.1±0.6*
Breathing frequency (breaths$\cdot$min^{-1})	16±5	22±5*	18±4	28±10*
Minute ventilation (L.min^{-1})	14.8±3.1	38.0±19.0*	27.4±7.9	56.9±16*
End-tidal CO_2 (mmHg)	35.5±4.1	27.8±5.4*	35.4±3.1	25.8±6.2*
Rib cage pulmonary volume/Inspiratory time (L.s^{-1})	0.2±0.1	0.5±0.1*	0.4±0.1	0.8±0.2*
Abdominal volume /Inspiratory time (L.s^{-1})	0.2±0.1	0.4±0.2*	0.4±0.2	0.7±0.3*
Abdominal volume/ Expiratory time (L.s^{-1})	0.2±0.1	0.4±0.3	0.3±0.2	0.6±0.3*

Data are presented as mean±SD; QB, quiet breathing; EVH, eucapcic voluntary hyperpnoea; *: p<0.05 compared to control

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4. Discussion

The major finding of the study is that application of pNIV during normal breathing and following EVH trials was not associated with circulatory compromise compared to quiet breathing, but instead was accompanied by increased central haemodynamic responses. This is most likely due to greater respiratory muscle metabolic requirement secondary to the fixed IPAP and EPAP causing an increase in breathing rate and thoracoabdominal volumes.

To our knowledge this is the first study investigating the physiological effects of intermittent application of pNIV in healthy individuals at rest and following high levels of sustained ventilation (EVH). In contrast to continuous or bi-level NIV methods, the VitaBreath device is designed for intermittent use primarily aiding recovery from breathlessness during activities of daily life in COPD patients [Hardy and Jasko 2015]. The primary objective of the device is to reduce the work of breathing during inspiration and keep the airways open during expiration in patients with COPD by providing fixed IPAP and EPAP [Hardy and Jasko 2015].

Previous studies [Montner, et al. 1994,Philip-Joet, et al. 1999,Valipour, et al. 2005,Leech and Ascah 1991] that applied different NIV methods incorporating varying IPAP and EPAP during spontaneous resting breathing in healthy individuals have had conflicting evidence in respect to circulatory responses. Application of continuous positive airway pressure (CPAP) exceeding 10 cmH$_2$O for 10-15 minutes, in the supine position or in head up tilt, was shown to cause a reduction in SV (by 12-28%) and CO (by 16-31%) [Montner, et al. 1994,Philip-Joet, et al. 1999,Valipour, et al. 2005]. Furthermore, application of BiPAP (IPAP = 12-15 cmH$_2$O and EPAP = 8-10 cmH$_2$O) for 15 minutes in the supine position decreased SV (by 12-13%) and CO (by 15-19%) [Philip-Joet, et al. 1999]. Increased intrathoracic pressure with CPAP and BiPAP are thought to reduce venous return, resulting in lower SV (Starling's law) and thus CO [Grubler, et al. 2017,Mahmood and Pinsky 2018,Kindgen-Milles, et al. 2002]. The lower pressures are sensed by the baroreceptors located on the carotid sinus and aorta [Looga 1997], causing increased sympathetic activity during static lung inflation manoeuvres [Macefield 1998] and following application of CPAP [Heindl, et al. 2001,Ikeda, et al. 1997]. However, in most studies heart rate was unaffected or increased [Montner, et al. 1994,Philip-Joet, et al. 1999,Valipour, et al. 2005,Leech and Ascah 1991]. In contrast to previous literature, we found a 27% increase in CO, with concomitant increases SV (10%) and HR (13%) when pNIV was applied. Use of the device made the respiratory muscles work harder on exertion (Table 3). As subjects were healthy they were able to accommodate the increase in respiratory muscle blood flow requirement by increasing HR, SV and thus CO.

In addition, it is well established that hyperventilation of room air with resultant hypocapnia invariably produces an increase in HR and CO [McGregor, et al. 1962]. The increase in CO is related to the increase in respiratory mechanical work per litre ventilation associated with the fall in carbon dioxide tension [McGregor, et al. 1962,Donevan, et al. 1962]. In our study, application of pNIV caused hyperventilation and substantial reductions in end-tidal carbon dioxide tension compared to control breathing (Table 3). Hyperventilation, even in absence of hypocapnia, may suppress baroreflex related inhibition of the sympathetic nervous system, causing the observed increases in SV and CO [Van De Borne, et al. 2000]. Furthermore, an additional factor that might affect cardiovascular responses is body position [Harms, et al. 2003]. In a number of studies [Montner, et al. 1994,Philip-Joet, et al. 1999,Leech and Ascah 1991] participants were in the supine position, whilst in our study they were seated

on a chair, most likely resulting in greater HR to facilitate venous return from the periphery to the heart [Harms, et al. 2003].

Although prolonged application of BiPAP and CPAP reduces SV and CO, this has no effect on blood pressure [Montner, et al. 1994,Philip-Joet, et al. 1999,Valipour, et al. 2005,Leech and Ascah 1991]. In fact, application of IPAP and EPAP between 10 to 15 cmH$_2$O did not cause any changes in right atrial, pulmonary arterial and systolic arterial pressures despite the reduction in SV and CO, most likely due to systemic vasoconstriction [Montner, et al. 1994,Philip-Joet, et al. 1999,Valipour, et al. 2005]. Our findings (Figure 2) are in accordance with these studies as we did not observe significant differences in blood pressure between the trials comparing pNIV to quiet breathing. The stability of blood pressure values despite the increase in SV and CO were most likely due to local respiratory and abdominal muscle vasodilation causing a decrease in vascular resistance which counteracted the increases in blood flow from increased CO [Robertson, et al. 1977].

During quiet breathing at the end of normal expiration alveolar and airway pressures are zero relative to atmospheric pressure and intrathoracic pressure is negative. However, when positive end-expiratory pressure (PEEP) is applied, the alveolar pressure remains positive throughout expiration [Brochard 2002] forcing the respiratory muscles to contract to an amount equal to PEEP before any changes in volume occurs, thus increasing the work of breathing [Zakynthinos, et al. 2000]. In addition, when PEEP is applied there is an increase in end-expiratory lung volume resembling the phenomenon of dynamic hyperinflation, causing greater intrathoracic pressures during expiration, thereby further increasing the work of breathing [Campbell 1959]. Our findings are indicative of end-expiratory DH, when pNIV was applied compared to control breathing (Figure 4 and Table 3). This finding in association with the increase in tidal volume and breathing frequency (Table 3) would most likely lead to increased work of breathing and thus respiratory muscle metabolic requirement.

Application of EPAP has previously shown to increase total and compartmental chest wall volumes in healthy older individuals [Cabral, et al. 2017,Frazao, et al. 2014]. In fact, the application of 10 cmH$_2$O EPAP significantly increased compartmental volumes [Cabral, et al. 2017,Frazao, et al. 2014] as well as muscle shortening velocity for all compartments [Cabral, et al. 2017,Frazao, et al. 2014]. In our study, the increase in tidal volume with pNIV was due to a higher contribution of the abdominal rib cage compartment (reflecting diaphragmatic action) but reduced contribution from the abdominal compartment (reflecting lower expiratory abdominal contribution) (Figure 5). The latter is compatible with end-expiratory DH when pNIV was applied compared to quiet breathing (Figure 4 and Table 3).

The stretch-shortening cycle is a well-accepted property of the muscular function by which the skeletal muscles can increase their power output [Bosco and Komi 1979,Cronin, et al. 2001,Komi 2000,Takarada, et al. 1997,Walshe, et al. 1998] and is another potential mechanism that can explain the greater work of breathing. The respiratory muscles can similarly increase their power output with manoeuvers in which respiratory muscle contraction is immediately preceded by an eccentric contraction of the respiratory muscles [Tzelepis, et al. 2005]. In our study, the high IPAP increased end-inspiratory chest wall volume when our participants breathed through the VitaBreath device. The greater end-inspiratory chest wall volume indicates a greater expansion of the chest wall stretching the respiratory muscles. This will allow respiratory muscles to produce greater force during expiration which

requires more energy, but it is essential in order to allow expiration against a high EPAP [Zakynthinos, et al. 2000].

Increase in respiratory muscle shortening velocity is associated with greater inspiratory rib cage and diaphragmatic pressures and generation of greater muscle power during application of expiratory flow limitation during exercise in healthy subjects [Aliverti, et al. 2002]. In our study we did not measure intrathoracic pressures, however muscle shortening velocity of the rib cage and abdominal muscles was increased. Considering that high IPAP and EPAP was provided by pNIV we can assume that intrathoracic pressures increased, collectively resulting in an increase in power generation of the respiratory muscles, energy requirement and CO.

Changes in the volumes of the rib cage compartment represent the action of the intercostal muscles and the diaphragm, whereas abdominal volume changes are affected by the function of the muscles of the abdominal wall [Aliverti and Pedotti 2002]. In previous studies application of PEEP in healthy individuals [Cabral, et al. 2017,Frazao, et al. 2014] reduced end-expiratory volume of the abdominal compartment allowing greater tidal volume. In our study end-inspiratory volumes of the rib cage pulmonary and abdominal compartments were increased indicating greater activation of the intercostal muscles and the diaphragm during inspiration (Figures 4 and 5). In contrast, there were no changes in end-expiratory volumes of the abdominal compartment, thereby reflecting decreased activation of the abdominal muscles during expiration (Figures 4 and 5).

When patients with COPD used pNIV during recovery periods between exercise bouts, we observed no circulatory compromise during the 1-min application of pNIV (9.9 ± 2.9 L.min^{-1}) compared to PLB (9.2 ± 2.8 L.min^{-1}) in recovery from exercise [Vogiatzis, et al. 2019]. Collectively the findings of the present study in healthy subjects and those in COPD [Vogiatzis, et al. 2019] preclude an adverse effect of pNIV on central hemodynamic responses in patients with potentially-limited cardiovascular regulation.

In the original study, in the majority of COPD patients the use of the device reduced dynamic hyperinflation most likely by keeping the airways open during expiration [Vogiatzis, et al. 2019]. Reduced dynamic hyperinflation had positive effects on stroke volume, and cardiac output during exercise [Vogiatzis, et al. 2011]. However, from the current study it seems that use of the device may increase respiratory muscle work compared to quiet breathing and hence may worsen breathlessness during its brief use in patients with compromised lung mechanics. Our original study [Vogiatzis, et al. 2019] reported that 6/24 patients had worsened dynamic hyperinflation when using the device compared to pursed lip breathing technique. This was accompanied by similar breathing discomfort levels. It is therefore apparent that the device may not benefit all COPD patients and thus caution should be taken before prescribing this device unvaryingly to all COPD patients.

Our data in healthy individuals suggest that the increased CO might be a result of the increased metabolic requirement of the respiratory muscles when patients used pNIV compared to quiet breathing. However, future studies should use OEP technology along with pleural and abdominal pressure measurements in order to investigate the acute effect of the application of pNIV on the work of breathing and respiratory muscle function.

Earlier studies have shown adverse effects of continuous NIV devices on central haemodynamic responses in healthy and diseased groups [Ambrosino, et al. 1993,Baratz, et al. 1992,Diaz, et al. 1997,Montner, et al. 1994,Naughton, et al. 1995,Philip-Joet, et al. 1999,Valipour, et al. 2005]. Our original study in patients with COPD showed no adverse

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effects of pNIV application, albeit in the setting of exercise where there are increasing demands on cardiac output [Vogiatzis, et al. 2019]. In the present study we investigated the acute mechanical/physiological effects of pNIV application on central hemodynamic regulation in the absence of confounding factors due to the disease. Whilst we found no circulatory compromise with pNIV application, we reported that breathing through high fixed airway pressures (8-18 cm H_2O) made the respiratory muscles work harder compared to quiet breathing. This finding is indicative of an apparent limitation of this new portable NIV device which may potentially worsen respiratory breathing discomfort in some respiratory patients. Our findings agree with studies employing other intermittent positive airway pressure (10 cmH_2O) devices, which revealed an increased work of breathing compared to spontaneous breathing [Mancebo, et al. 1995] in healthy individuals. Hence, the relevance of the present study in healthy subjects is that when portable NIV is to be proposed for spontaneously breathing patients with acute respiratory failure, caution should be taken to avoid worsening of dyspnoea induced by the device.

Study Limitations

In this study we did not assess the work of breathing during inspiration or expiration when pNIV was applied. This is an important limitation given that the VitaBreath device is built to reduce the work of breathing during inspiration and maintain the airways open during expiration in an attempt to reduce DH. In addition, non-adjustable IPAP and EPAP may have enhanced the work of breathing, and worsen dynamic hyperinflation in our healthy population; this possibility was not investigated in the present study. Another limitation of our study is that the duration of pNIV application was chosen to be short (to reflect the actual use of the device by patients in every day life as previously described [Vogiatzis, et al. 2019] and therefore the cardiovascular and respiratory systems had limited time to be adversely affected by the imposed IPAP and EPAP. Use of falconia tubing during the EVH trials may have increased the resistance to breathing to a greater extent than breathing room air. Our intention was to investigate the acute mechanical/physiological effects of pNIV application on central hemodynamic regulation in the absence of confounding factors due to the disease. These findings may not be fully inferable to the clinical setting, nevertheless they yield important physiological knowledge of the effects of a new device. We share the approach of testing a new device in healthy volunteers with several studies where application of continuous or bi-level IPAP and EPAP at rest [Montner, et al. 1994,Philip-Joet, et al. 1999,Valipour, et al. 2005] or at high levels of respiration [Stark-Leyva, et al. 2004], have had diverse results either causing reductions in SV and CO [Grubler, et al. 2017,Mahmood and Pinsky 2018] or no significant circulatory effects [Leech and Ascah 1991]. Given that out original study [Vogiatzis, et al. 2019] was not designed to provide evidence as to whether there would be a positive or negative hemodynamic effect of pNIV in COPD patients, the current investigation may justify this first *in vivo* evaluation of intermittent pNIV application on central hemodynamic regulation in healthy volunteers.

5. Conclusions

Application of pNIV provided by the VitaBreath device does not cause adverse haemodynamic effects in healthy individuals. In contrast the application of high, short-term,

fixed end-inspiratory and end-expiratory pressures increased haemodynamic responses, most likely reflecting increased respiratory muscle requirement.

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Figure Legends

Figure 1. Study protocol. a) Normal breathing, b) Eucapnic voluntary hyperpnoea. Within the two protocols (a and b) each participant performed two trials with and without the application of pNIV in a balanced order.
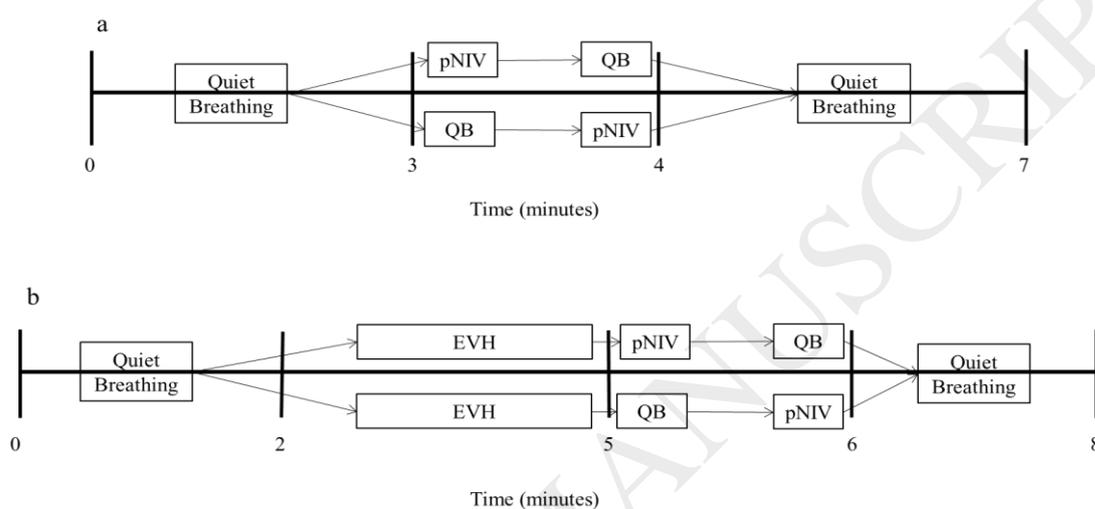
Figure 1

Figure 2. Effect of the application of pNIV (closed circles) compared to quiet breathing (open circles) on stroke volume (a), heart rate (c), cardiac output (e), systolic (b), diastolic (d) and mean blood pressure (f) during the EVH trials. Data are presented as mean ± standard error of the mean (SEM). * $p < 0.05$ pNIV vs quiet breathing (QB).
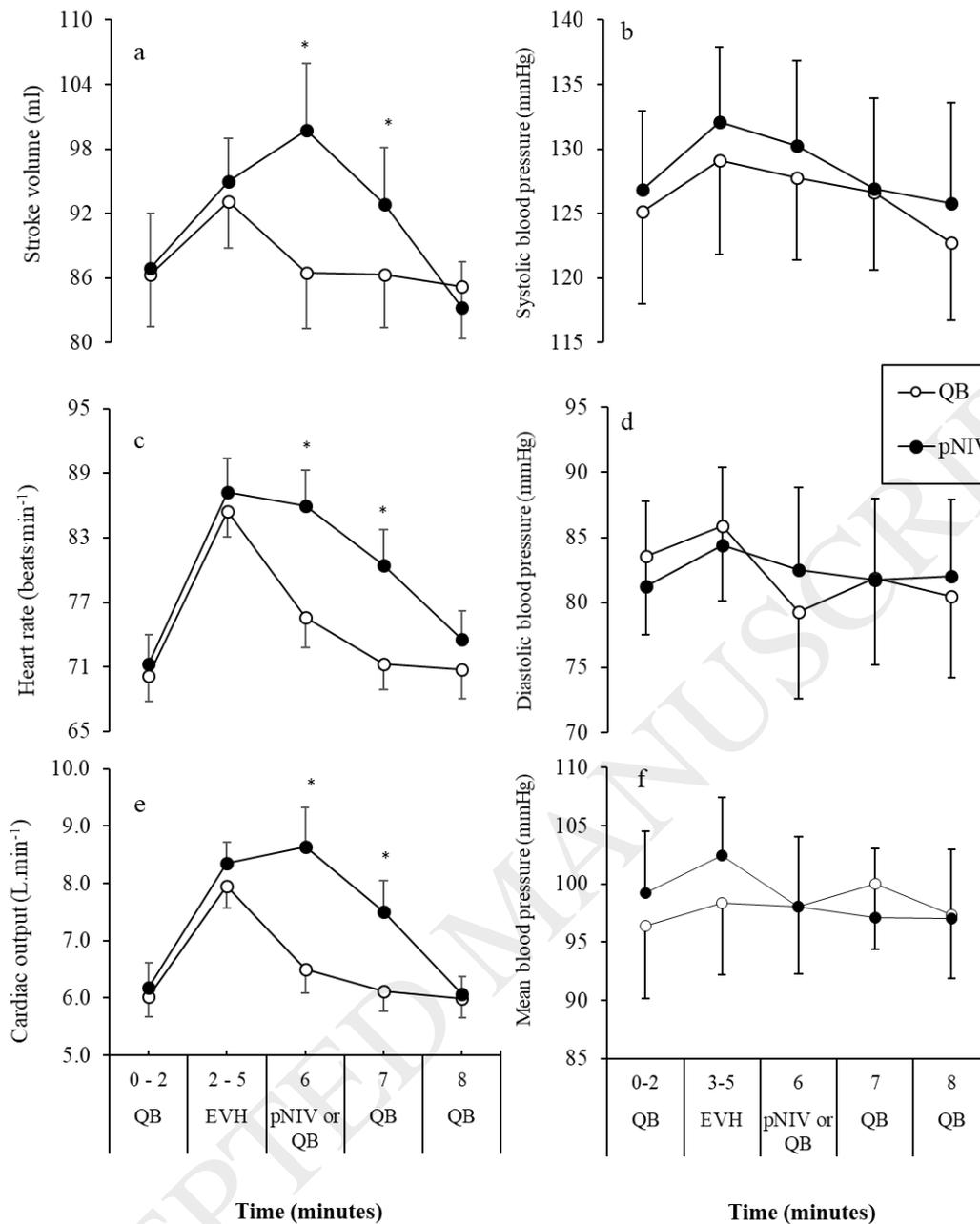
Figure 2

Figure 3. Typical example of the changes in end-inspiratory and end-expiratory chest wall volumes with the application of pNIV during: a) normal breathing and b) EVH trials. QB: quiet breathing, EVH: eucapnic voluntary hyperpnoea, pNIV: application of VitaBreath, EI: end-inspiratory volume, EE: end-expiratory volume.
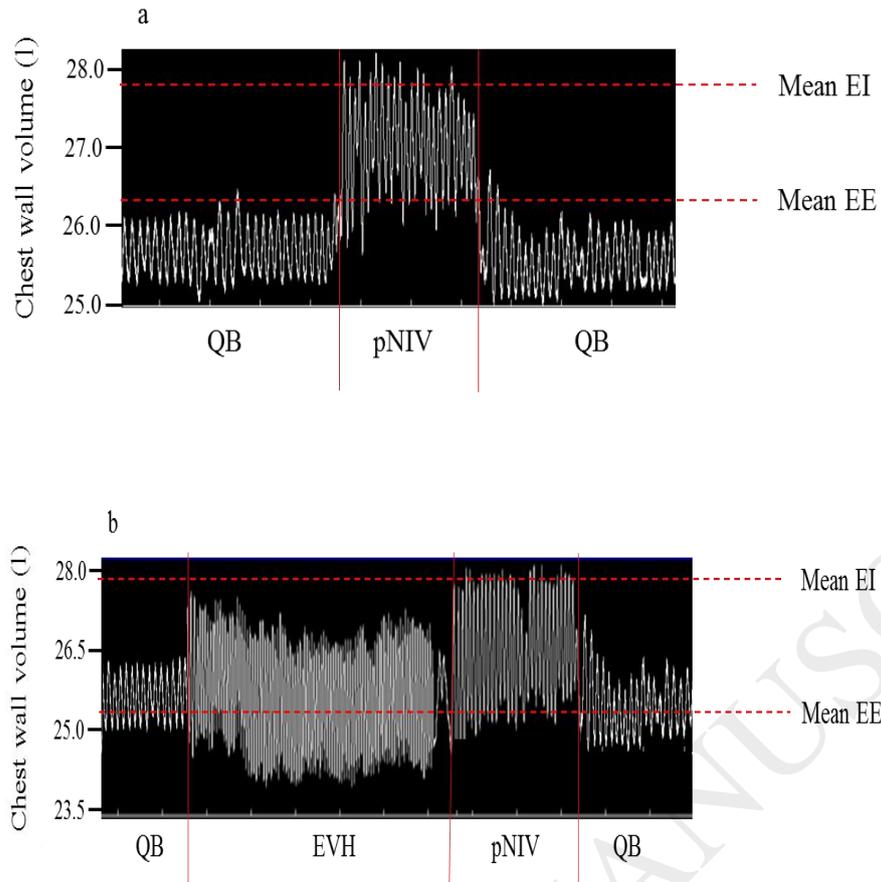
Figure 3

Figure 4. Effect of the application of pNIV (closed symbols) compared to quiet breathing (open symbols) on total thoracoabdominal volume (CW: a), rib cage pulmonary volume (RCp: b), rib cage abdomen (RCa: c) and abdominal volume (Ab: d) during the EVH trials. Data are presented as mean ± standard error of the mean (SEM). * p<0.05 pNIV vs quiet breathing (QB).
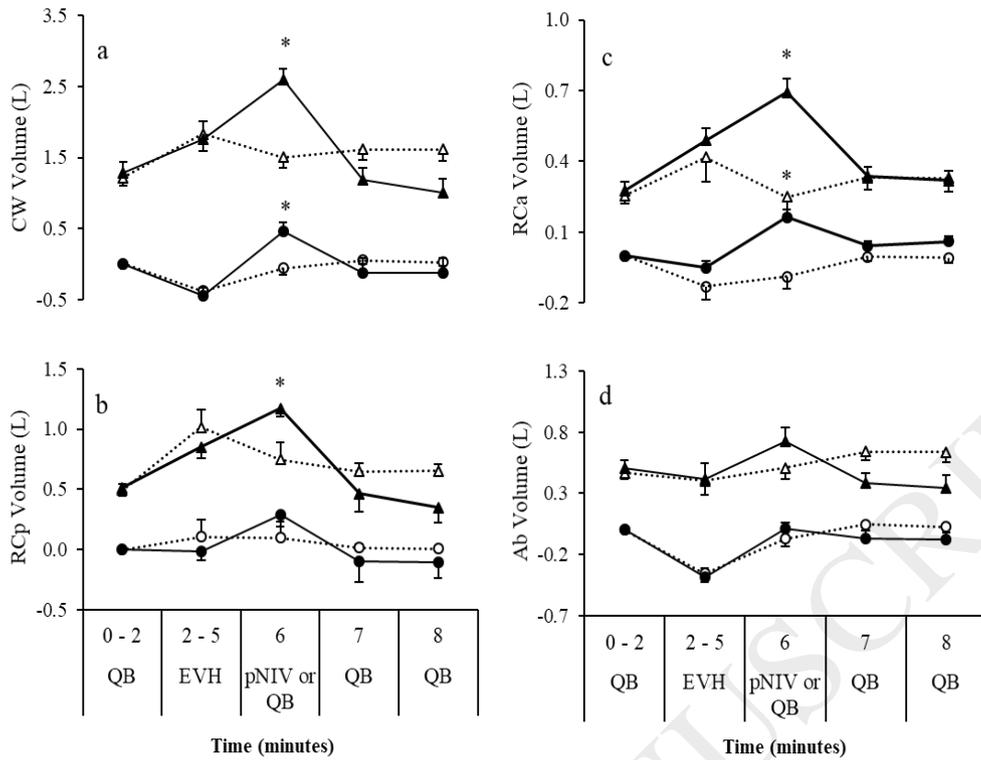
Figure 4

Figure 5. Effect of the application of pNIV compared to quiet breathing on compartmental distribution of tidal volume during: a) normal breathing and b) EVH trials. QB: quiet breathing, pNIV: portable non-invasive ventilation, EVH: eucapnic voluntary hyperpnoea, CW: chest wall, Rcp: rib cage pulmonary compartment, Rca: rib cage abdomen compartment, Ab: abdominal compartment, * p<0.05 pNIV vs QB; $<0.05 pNIV vs quiet breathing (QB).

Figure 5