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Effect of heliox breathing on flow limitation in chronic heart failure patients

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ABSTRACT: Patients with chronic heart failure (CHF) exhibit orthopnoea and tidal expiratory flow limitation in the supine position. It is not known whether the flow-limiting segment occurs in the peripheral or central part of the tracheobronchial tree. The location of the flow-limiting segment can be inferred from the effects of heliox (80% helium/20% oxygen) administration. If maximal expiratory flow increases with this low-density mixture, the choke point should be located in the central airways, where the wave-speed mechanism dominates. If the choke point were located in the peripheral airways, where maximal flow is limited by a viscous mechanism, heliox should have no effect on flow limitation and dynamic hyperinflation.

Tidal expiratory flow limitation, dynamic hyperinflation and breathing pattern were assessed in 14 stable CHF patients during air and heliox breathing at rest in the sitting and supine position.

No patient was flow-limited in the sitting position. In the supine posture, eight patients exhibited tidal expiratory flow limitation on air. Heliox had no effect on flow limitation and dynamic hyperinflation and only minor effects on the breathing pattern.

The lack of density dependence of maximal expiratory flow implies that, in CHF patients, the choke point is located in the peripheral airways.

KEYWORDS: Chronic heart failure, dynamic hyperinflation, expiratory flow limitation, heliox

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STATEMENT OF INTEREST
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Tidal expiratory flow limitation (EFL) at rest has been detected in both sitting and supine spontaneously breathing patients with acute heart failure [1], and in patients with chronic heart failure (CHF) in the supine position alone [2]. At present, it is not known whether, in CHF, the choke point is located in the central or peripheral part of the tracheobronchial tree. Such localisation can be accomplished by studying the density dependence of maximal expiratory flow, and, consequently, the mechanisms by which tidal EFL develops. According to the wave-speed theory, flow limitation results from the coupling between airway compliance and convective acceleration of gas [3]. Since the pressure drop due to convective acceleration is density-dependent, the wave-speed theory states that the maximal expiratory flow increases with decreasing gas density. Flow limitation can also result from the coupling between airway compliance and viscous pressure losses [3]. If flow is limited by this viscous mechanism, the maximal expiratory flow is not expected to change when gas density changes. When the maximal flow is limited at wave speed (as is the case in normal subjects at high lung volume), the flow-limiting segment is located in the central airways. In contrast, when the maximal flow is limited by a viscous mechanism (as is the case in normal subjects at low lung volume), the flow-limiting segment is located in the peripheral airways [4].

The aim of the present investigation was to assess whether the tidal EFL exhibited by CHF patients in the supine position is located centrally or peripherally. To this end, the density dependence of EFL was studied by replacing inspired air with heliox, a gas mixture three times less dense than air. The effect of heliox was assessed in terms of maximal expiratory flows, dynamic hyperinflation and breathing pattern, as previously described in patients with stable chronic obstructive pulmonary disease (COPD) [5].

MATERIALS AND METHODS

Stable ambulatory CHF patients (n=14; one female) with a mean±SEM age of 57±3 yrs were studied. No patient had been hospitalised within the 20 days preceding the study. Heart failure was defined as symptomatic left ventricular dysfunction with a left ejection fraction of <0.45 documented by bidimensional echocardiography. The congestive heart failure was post-ischaemic in nine patients. No patient exhibited peripheral oedema. Three patients were current smokers, three nonsmokers and eight ex-smokers.

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At the time of the study, 12 patients were being treated with diuretics, eight with β-blockers and four with digoxin. On the experimental day, Weber class was determined using cardiopulmonary exercise testing [6]. Three patients were Weber class A (maximal oxygen uptake ($V'_{O_2,max}$) of >20 mL·kg^{-1}·min^{-1}), four Weber class B ($V'_{O_2,max}$ of 16–20 mL·kg^{-1}·min^{-1}), five Weber class C ($V'_{O_2,max}$ of 10–15 mL·kg^{-1}·min^{-1}) and two Weber class D ($V'_{O_2,max}$ of <10 mL·kg^{-1}·min^{-1}). Predicted $V'_{O_2,max}$ were computed using Wasserman's equations [7]. Patients with primary pulmonary, neurological or myopathic diseases were excluded. In particular, to avoid the possible confounding effects of subclinical COPD, patients were also excluded if their forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) was <75% [8]. To this end, before the beginning of the experiments, spirometry was performed using standard methods and procedures [9], using a mass flow sensor (Vmax 22; SensorMedics Co., Yorba Linda, CA, USA), with reference values being those of the European Coal and Steel Community [9]. The study was approved by the Ethics Committee of Evangelismos General Hospital (Athens, Greece) and each patient gave informed consent.

The severity of chronic dyspnoea was assessed using the modified Medical Research Council (MMRC) scale [10].

Patients were investigated while breathing air and 10 min after equilibration with heliox. Measurements were carried out first in the seated and then in the supine position (after 10 min in the supine position). Air and heliox breathing were performed in random order.

The assessment of tidal EFL was carried out by means of the negative expiratory pressure (NEP) method [11]. Subjects, wearing a nose clip, breathed quietly through a flanged mouthpiece, a heated pneumotachometer (3830A; Hans Rudolph, Kansas City, MO, USA) connected to a differential pressure transducer (Celesco LCVR-0005; Raytech Instruments, Vancouver, BC, Canada) and a low resistance two-way valve (2600; Hans Rudolph). The expiratory port of the valve was connected to a Venturi device and the inspiratory port to a shutter (RV-12; AeroMech Devices, Almonte, ON, Canada). The Venturi device was connected via a solenoid valve to a high-pressure source and a regulator allowed for a pre-set pressure (-5 cmH_2O) at the airway opening that was measured with a pressure transducer (Celesco LCVR-0100; Raytech Instruments). The shutter was connected through a three-way stopcock to the ambient air or to a large plastic bag containing humidified heliox at ambient temperature. The patient was unaware of the gas mixture they were breathing. The pneumotachograph, calibrated with a 3-L syringe filled with the test gas, was linear over the experimental flow range. Pressure and flow signals were amplified, low-pass filtered at 50 Hz and digitised at 100 Hz by a 16-bit analogue-to-digital converter (Direc Physiologic Recording System; Raytech Instruments). The volume was obtained by numerical integration of the flow signal. The digitised data were stored on a computer and subsequently analysed (LabVIEW Software; National Instruments, Austin, TX, USA).

In all cases, several NEP tests were performed at intervals of 10–15 breaths, with the preceding expiration serving as control. The manoeuvres were discarded if superimposability between the inspiratory part of the flow–volume loop of the control and test breaths was poor. Patients were classified as non-flow-limited, if the application of NEP increased expiratory flow over the entire range of the control tidal volume, or flow-limited, if the control and test expiratory flow–volume loops superimposed at least in part (fig. 1). Two or three breaths after each NEP test, the subjects inspired to total lung capacity (TLC) for assessment of inspiratory capacity (IC), and alignment of tidal flow–volume curves with respect to TLC. IC was measured as the difference between TLC and the end-expiratory volume of the control breath, and used to assess changes in dynamic hyperinflation, an approach that has been shown to be reliable in COPD patients [12]. In each patient and condition, a minimum of four acceptable IC manoeuvres, and NEP applications were performed.

Under all experimental conditions, three FVC manoeuvres were performed and the breathing pattern was assessed over a 3-min period. Dyspnoea was measured under each experimental condition using a 100-mm visual analogue scale (VAS).

Data, presented as mean±SEM, were analysed using a mixed between–within-groups ANOVA. The correlation between MMRC score and routine spirometric measurements was examined using the nonparametric Spearman rank correlation. Statistical significance was taken at a p-value of $\leqslant 0.05$.

RESULTS

Sitting breathing air

Table 1 shows the anthropometric characteristics and baseline lung function of the patients in the sitting position. FVC, FEV_1, expiratory reserve volume (ERV) and IC were reduced compared to predicted values. In this posture, none of the patients exhibited tidal EFL. Dyspnoea at rest was modest, as indicated by the low VAS score (12±2 mm). The significant correlation coefficients of MMRC *versus* the respiratory variables are shown in table 2. MMRC correlated with percentage predicted IC, FVC and FEV_1 (p=0.006, 0.009 and 0.038, respectively), as well as with age (p=0.042) and percentage predicted $V'_{O_2,max}$ (p=0.001).

Supine breathing air

Shifting to the supine position caused the FVC to decrease (change (Δ) in FVC -0.20±0.04 L; p<0.01) and, as expected, IC to increase (ΔIC 0.42±0.09 L; p<0.01), whereas breathing pattern remained unchanged. In this position, eight (57%) patients became flow-limited. These patients had lower ERVs than the non-flow-limited patients (0.25±0.04 *versus* 0.49±0.10 L, respectively; p=0.02) (table 3; fig. 2). Dyspnoea sensation tended to increase from the sitting to the supine position, but this increase was significant only in those patients who became flow-limited (ΔVAS 7±1 mm; p<0.01). Since tidal EFL occurred in the supine position, anthropometric and spirometric data obtained in the sitting position were retrospectively reviewed in order to assess for any difference between patients who became or did not become flow-limited (table 1). The flow-limited patients showed significantly lower FVCs than non-flow-limited patients (71±6 *versus* 92±4% pred, respectively; p=0.02) and a higher body mass index (BMI) than the latter (30±1 *versus* 25±1 kg·m^{-2}, respectively; p<0.01). No difference was found in smoking history between

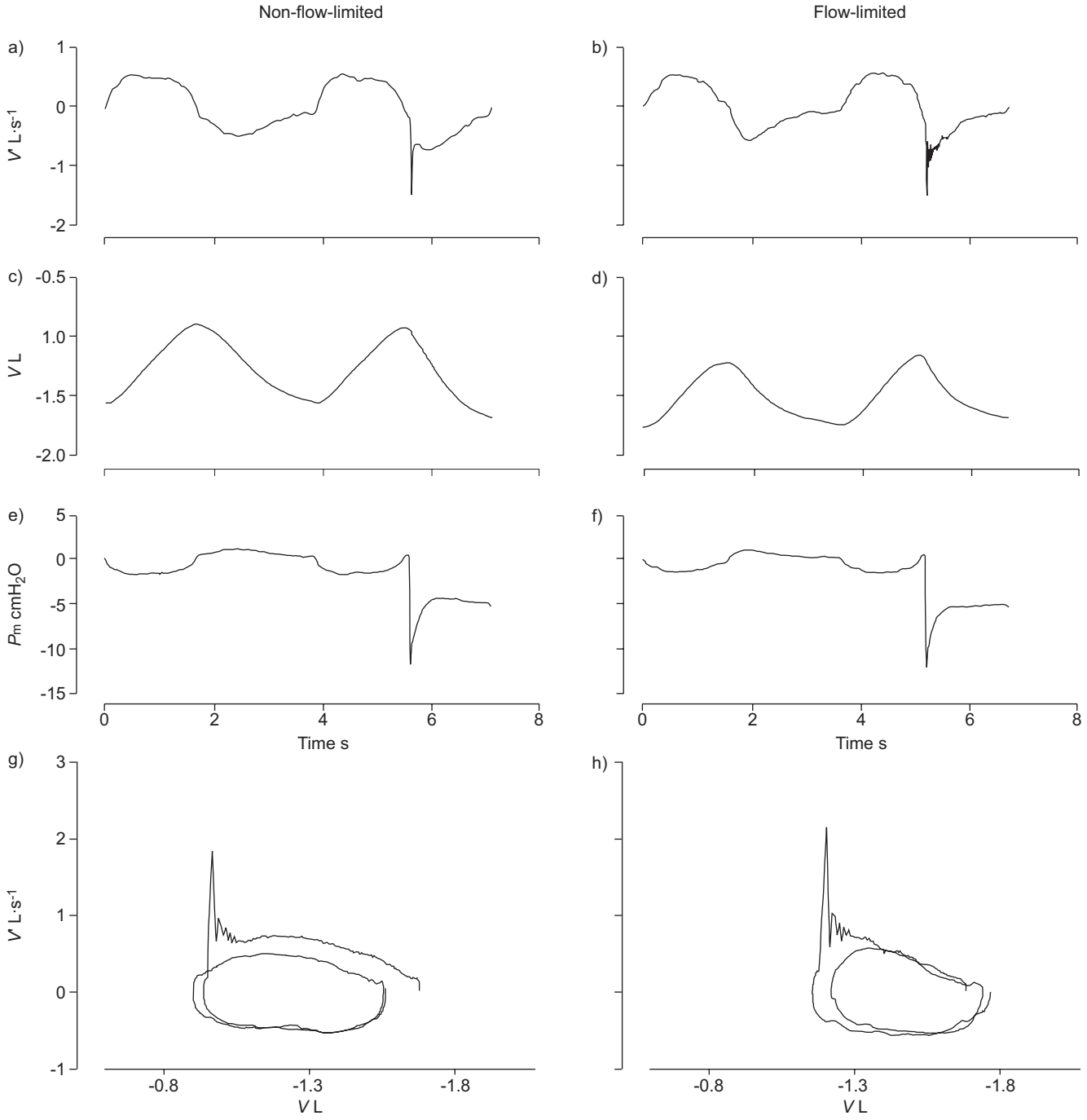

FIGURE 1. Example of a non-flow-limited and a flow-limited chronic heart failure patient breathing air in the supine position. Time course of: a, b) flow ($\dot{V}$); c, d) volume (V; from total lung capacity); and e, f) mouth pressure (P_m) with (second breath) and without negative expiratory pressure application. g, h) corresponding flow–volume curves.

the two groups of patients. In this regard, it is interesting that all three nonsmokers in the present study became flow-limited in the supine position.

Effect of heliox

In the sitting position, heliox had no effect on IC. Table 3 shows the respiratory parameters in the supine position on air and heliox. Heliox did not abolish EFL in any instance, and did not change IC (fig. 3). Heliox caused a modest reduction in inspiratory time (0.12 ± 0.04 s; $p<0.01$) and dyspnoea sensation (ΔVAS -1.4 ± 0.04 mm; $p<0.01$), independent of posture and flow limitation.

DISCUSSION

The new finding of the present study is that, in all CHF patients who were flow-limited while breathing air at rest, heliox had no effect on flow limitation and dynamic hyperinflation, assessed as ΔIC. Consequently, in these patients, tidal

TABLE 1 Anthropometric and routine lung function data of air-breathing seated chronic heart failure patients with or without supine tidal expiratory flow limitation

	Total	Flow-limited	Non-flow-limited
Subjects	14	8	6
M/F	13/1	8/0	5/1
Age yrs	57±3	61±3	51±6
Height m	1.76±0.01	1.78±0.02	1.74±0.02
BMI kg·m^{-2}	28±1	30±1*	25±1
MMRC score	1.9±0.3	2.3±0.3	1.3±0.4
Dyspnoea VAS mm	12±2	14±2	8±3
Smokers/nonsmokers	11/3	5/3	6
$V'O_{2,max}$ mL·kg^{-1}·min^{-1}	16.1±1.5	14.4±1.7	18.5±2.7
$V'O_{2,max}$ % pred	56±5	52±5	62±8
AT mL·min^{-1}·kg^{-1}	11.9±1.3	10.4±1.1	13.8±2.6
FVC % pred	80±5	71±6*	92±4
FEV_1 % pred	72±4	63±4*	84±4
FEV_1/FVC % pred	94±2	92±2	95±3
IC % pred	73±5	66±6	81±6
ERV % pred	80±10	65±12	100±14

Data are presented as n or mean±SEM. M: male; F: female; BMI: body mass index; MMRC: modified Medical Research Council; VAS: visual analogue scale; $V'O_{2,max}$: maximal oxygen uptake; AT: anaerobic threshold; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; IC: inspiratory capacity; ERV: expiratory reserve volume; % pred: percentage of the predicted value. *: $p<0.05$ *versus* non-flow-limited patients.

EFL arose from abnormalities within the peripheral part of the tracheobronchial tree, as it occurs in COPD patients at rest [5].

Patient population

The present patients exhibited a spirometric pattern compatible with restriction, since FVC, FEV_1, ERV and IC were reduced, whereas the FEV_1/FVC ratio was normal. Several studies on CHF patients have documented a restrictive pattern of pulmonary impairment [2, 13], caused by an increase in vascular or interstitial lung water [14, 15], heart enlargement [13, 16] and a decrease in the force of the inspiratory muscles [17].

Dyspnoea sensation at rest (table 1) in the sitting position was modest, as previously reported in stable CHF patients [2]. Age and $V'O_{2,max}$ were independent predictors of MMRC; the dependence on age could be related to the age-dependent impairment of the respiratory system [18]. Since the MMRC scale measures the degree of breathlessness related to daily activities, it is not surprising that, in the present patients, the best correlation of the MMRC score was with $V'O_{2,max}$ (table 2). The MMRC score also correlated closely with IC ($p=0.006$). A reduction in IC can reflect an increase in functional residual capacity due to loss of lung recoil, as in COPD patients [5], or a decrease in TLC because of an increased volume of nonpulmonary intrathoracic structures, as in CHF patients [17]. It may be speculated that, in the latter case, the volume of the chest wall could even be increased, depending on the combined effect of the volumetric increase in nonpulmonary intrathoracic structures and the decrease in lung compliance.

TABLE 2 Significant correlations of modified Medical Research Council score with anthropometric and respiratory parameters in seated chronic heart failure patients

	r_S	p-value
Age yrs	0.548	0.042
$V'O_{2,max}$ % pred	-0.782	0.001
FVC % pred	-0.665	0.009
FEV_1 % pred	-0.559	0.038
IC % pred	-0.693	0.006

$V'O_{2,max}$: maximal oxygen uptake; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; IC: inspiratory capacity; % pred: percentage of the predicted value.

In CHF patients, the inspiratory muscles, therefore, would work under a condition of mechanical disadvantage, increasing the dyspnoea sensation, especially during exercise, when dynamic hyperinflation may develop [19].

Tidal flow limitation

Tidal EFL was absent in all 14 CHF patients while breathing air in the sitting position. In contrast, eight (57%) patients became flow-limited when supine. One major factor involved in the development of tidal EFL in the supine position is the reduction in lung recoil secondary to the decrease in lung volume that occurs because of the expiratory action of the abdomen and shift of blood into the thoracic cavity. The changes in ERV occurring in the present patients should closely reflect those in functional residual capacity, since changes in residual volume between the upright posture and recumbency are very small in normal subjects, and the residual

TABLE 3 Inspiratory capacity (IC), expiratory reserve volume (ERV), dyspnoea and breathing pattern in supine chronic heart failure patients with or without tidal expiratory flow limitation

	Flow-limited		Non-flow-limited	
	Air	Heliox	Air	Heliox
Subjects n	8		6	
IC L	2.68±0.21	2.64±0.20	3.11±0.26	3.08±0.27
ERV L	0.25±0.05*	0.26±0.05*	0.49±0.10	0.57±0.15
t_I s	1.47±0.13	1.37±0.11#	1.58±0.16	1.49±0.19#
t_E s	1.95±0.10	1.98±0.14	2.06±0.31	2.19±0.39
V_T L	0.70±0.05	0.73±0.06	0.65±0.08	0.71±0.13
V_T/t_E L·s^{-1}	0.36±0.03	0.38±0.03	0.35±0.05	0.36±0.06
Dyspnoea VAS mm	21±3	19±2#	11±4	9±3#

Data are presented as mean±SEM. t_I: inspiratory time; t_E: expiratory time; V_T: tidal volume; V_T/t_E: mean expiratory flow; VAS: visual analogue scale. *: $p<0.05$ *versus* non-flow-limited patients breathing air or heliox; #: $p<0.05$ *versus* air.

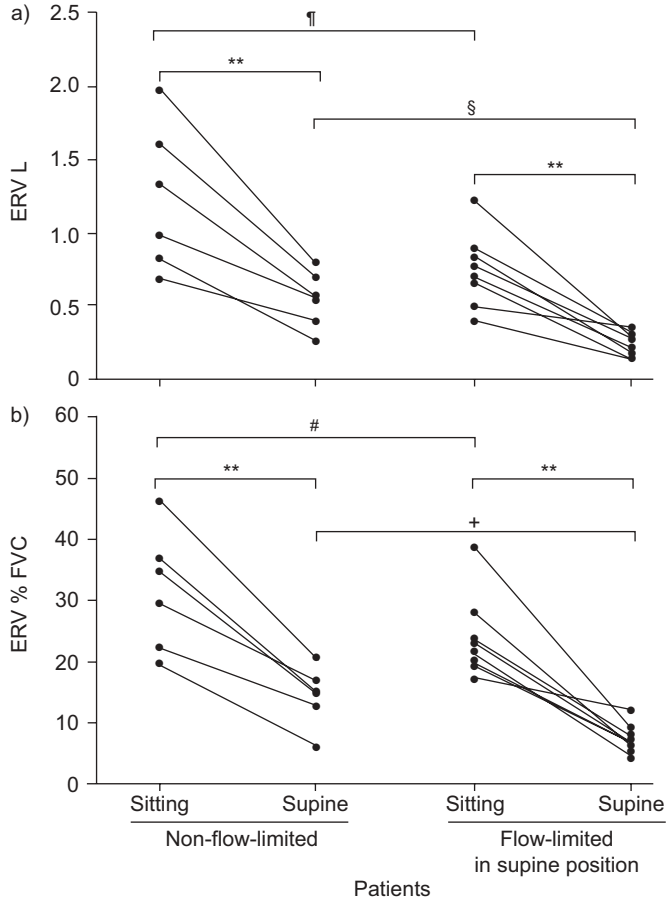

FIGURE 2. Mean expiratory reserve volume (ERV) of 14 chronic heart failure patients breathing air sitting and supine with (n=8) or without (n=6) tidal expiratory flow limitation in the supine position: a) absolute value; and b) relative to forced vital capacity (FVC) in sitting position. No patients were flow-limited while sitting. **: $p<0.01$; #: $p=0.11$; ¶: $p=0.04$; +: $p=0.03$; §: $p=0.02$.

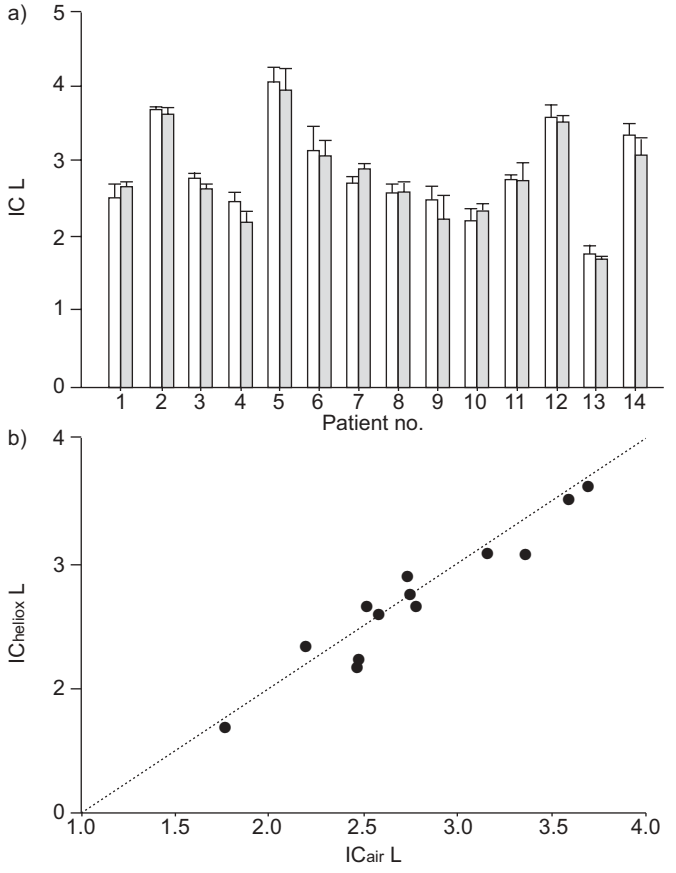

FIGURE 3. a) Mean inspiratory capacity (IC) during air (□) and heliox (■) breathing in 14 supine chronic heart failure patients. Vertical bars represent half ranges. b) Relationship between IC on heliox (IC_{heliox}) and air (IC_{air}) in the same patients (·····: identity line).

volume in seated CHF patients is within normal limits [17, 20]. In stable CHF patients, the ERV can be reduced even in the sitting position (table 1), presumably because of the increased volume of the heart, blood vessels and pulmonary interstitium [2, 13]. As lung volume decreases, maximal expiratory flows decrease because of the decreased lung recoil, which is a major determinant of maximal flows. In CHF patients, the decrease in maximal flows with decreasing lung volume is more prominent than in normal subjects; indeed, it has been shown that maximal expiratory flows can be markedly reduced (65% pred) in the lower 25% of FVC without any substantial fall in FEV_1 (92% pred) [21]. This could have occurred in the present patients, since, in the supine position, the flow-limited patients had a lower ERV than non-flow-limited subjects (table 3; fig. 2a), even when ERV was expressed as a percentage of standing FVC (fig. 2b). Moreover, the flow-limited patients were overweight; this might have contributed to the decrease in ERV, as shown by the significant correlation between BMI and ERV ($p=0.03$), thus favouring the occurrence of EFL. Mild obesity alone, however, cannot explain the high frequency of tidal EFL in supine CHF patients. Indeed, in a group of 16 healthy subjects with a BMI of 36 ± 1 kg·m^{-2} (range 30–40 kg·m^{-2}), only three exhibited EFL when supine, an incidence significantly lower than that of CHF patients ($p<0.01$). Moreover no EFL was observed in nine normal supine subjects with a BMI of 42 ± 10 kg·m^{-2} [22].

Effects of heliox breathing

In the absence of tidal EFL, no dynamic hyperinflation should be present, and hence no change in IC should occur while breathing heliox. This was the case in six patients who were non-flow-limited in the supine position and in all patients in the sitting posture. In the presence of EFL, dynamic hyperinflation can develop, especially if the respiratory frequency is higher than normal, as is usually the case in CHF patients [2, 23]. Heliox might decrease dynamic hyperinflation by increasing the maximal expiratory flows if the choke point were located in the central airways and set by the wave-speed mechanism. In the present eight patients who were flow-limited in the supine position, heliox neither increased IC nor changed the duration of expiration and mean expiratory flow. This lack of density dependence of the expiratory flow indicates that the choke point is located in the peripheral airways, where the viscous mechanism dominates [3, 4]. The location of the flow-limiting segment in the peripheral airways

implies modifications of their mechanical properties, namely an increase in resistance, compliance or both. Unfortunately, there is no information about the functional state of the peripheral airways in CHF patients.

When respiratory resistance was investigated using the forced oscillation technique, an enhanced frequency dependence of respiratory resistance was detected [20, 24], a finding that is usually related to peripheral airways impairment. However, the fact that a similar frequency dependence has been found in patients with upper airway obstruction [25] makes this interpretation problematic. In seated CHF patients, total or pulmonary resistance is normal [23] or moderately elevated [20, 24]. In contrast, in the supine position, the increase in respiratory resistance is always greater than normal [20, 23]. This suggests that the increase in respiratory resistance occurs due to the decrease in lung volume that takes place on switching from the sitting to the supine position and/or vascular engorgement and interstitial oedema, all factors which should mainly affect peripheral airways. In this connection, it should be noted that the effect of vascular engorgement and interstitial oedema on peripheral resistance depends upon pulmonary volume. Indeed, ISHII *et al.* [26] found that, in open-chest dogs, the increase in peripheral airway resistance with vascular engorgement and interstitial and alveolar oedema was markedly reduced and eventually abolished by increasing lung volume. It seems likely that, in at least some of the present supine patients, vascular engorgement was increased. Indeed, it has been shown that, in ~50% of CHF patients, pulmonary capillary wedge pressure increases when switching from the sitting to the supine position [27]. Conversely, studies performed in animal models have provided contrasting results; vascular engorgement and interstitial oedema resulted in a decreased small airway cross-section and presumably increased pulmonary resistance when airway calibre was measured using high-resolution computed tomography [28], but not when it was assessed using histological preparations [29]. Although vagally mediated bronchocostriction might also have contributed to the increase in respiratory resistance in the supine position, it has been shown that administration to CHF patients of large doses of ipratropium, a muscarinic antagonist, attenuates the increase in pulmonary resistance only slightly [20].

While breathing heliox, there was a significant reduction in dyspnoea sensation and inspiratory duration, regardless of posture or EFL. However, these changes were very small and devoid of clinical significance.

Whatever the precise nature of the tidal EFL exhibited by CHF patients in the supine position, the functional alterations must occur at a peripheral level, because of the absence of density dependence.

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