

Effect of Heliox Breathing on Flow Limitation in Chronic Heart Failure Patients

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ABSTRACT

Patients with chronic heart failure (CHF) exhibit orthopnea and tidal expiratory flow limitation in the supine position. It is unknown 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% He, 20% O₂) 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 sitting and supine position.

No patient was flow limited in the sitting position. In the supine posture 8 patients exhibited tidal expiratory flow limitation on air. Heliox had no effect on flow limitation, dynamic hyperinflation and only minor effects on the breathing pattern.

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

INTRODUCTION

Tidal expiratory flow limitation (EFL) at rest has been detected in spontaneously breathing patients with acute heart failure both sitting and supine (1) and in patients with chronic heart failure (CHF) in the supine position only (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 localization 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 will increase 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 is 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 has been 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 (5).

MATERIALS AND METHODS

Fourteen stable ambulatory CHF patients (one woman) with a mean age of 57 ± 3 (SE) years were studied. No patient had been hospitalized 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. Congestive heart failure was post-ischemic in 9 patients. No patient had peripheral edema. Three patients were current smokers, 3 non smokers and 8 ex-smokers. At the time of the study 12 patients were being treated with diuretics, 8 with β -blockers and 4 with digoxin. On the experimental day, Weber class was determined by cardiopulmonary exercise testing (6): 3 patients were Weber class A (maximal oxygen uptake ($V'O_2\text{max}$) greater than $20 \text{ mL kg}^{-1} \text{ min}^{-1}$); 4 patients were Weber class B ($V'O_2\text{max}$ between 16 and $20 \text{ mL kg}^{-1} \text{ min}^{-1}$); 5 patients were Weber class C ($V'O_2\text{max}$ between 10 and $15 \text{ mL kg}^{-1} \text{ min}^{-1}$), and 2 patients were Weber class D ($V'O_2\text{max}$ less than $10 \text{ mL kg}^{-1} \text{ min}^{-1}$). The predicted values of $V'O_2\text{max}$ were computed using Wasserman's equations (7). Patients with primary pulmonary, neurologic or myopathic diseases were excluded. In particular, to avoid the possible confounding effects of subclinical chronic obstructive pulmonary disease, patients were also excluded if their FEV₁/FVC was lower than 75% (8). To this end, before the beginning of the experiments, spirometry was performed with standard methods and procedures (9), using a mass flow sensor (Vmax 22; SensorMedics Co., Yorba Linda, CA, USA), reference values being those of the European Coal and Steel Community (9). The study was approved by the local ethical committee and each patient gave informed consent.

The severity of chronic dyspnea was assessed with the modified Medical Research Council (mMRC) scale (10).

Patients were investigated while breathing air and 10 minutes after equilibration with heliox. Measurements were carried out first seated and next supine (after 10 minutes of decubitus). Air and heliox breathing were performed in random order.

The assessment of tidal EFL was done by means of the negative expiratory pressure (NEP) method (11). Subjects, wearing a noseclip, breathed quietly through a flanged mouthpiece, a heated pneumotachometer (3830A; Hans Rudolph; Kansas City, MO) 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 preset pressure ($-5 \text{ cmH}_2\text{O}$) 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 he was 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 digitized at 100 Hz by a 16-bit AD converter (Direc Physiologic recording System; Raytech Instruments). Volume was obtained by numerical integration of the flow signal. The digitized data were stored on a computer and subsequently analyzed (LabVIEW Software; National Instruments; Austin, TX).

In all cases several NEP tests were performed at intervals of 10 to 15 breaths, with the preceding expiration serving as control. The maneuvers were discarded if the superimposition between the inspiratory part of the flow-volume (V' -V) loop of control and test breath 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 (V_T) (Fig. 1, *panel A*), or flow limited, if the control and test expiratory V' -V loops superimposed at least in part (Fig. 1, *panel B*). Two to three breaths after each NEP test, the subjects inspired to total lung capacity (TLC) for the assessment of inspiratory capacity (IC), and alignment of tidal V' -V 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 4 acceptable IC maneuvers, and NEP applications were performed.

Under all experimental conditions, 3 forced vital capacity (FVC) maneuvers were performed and the breathing pattern was assessed over a 3 minutes period. Dyspnea was measured in each experimental condition using a 100 mm visual analog scale (VAS).

Data, presented as mean \pm SE, were analyzed using a mixed between-within groups ANOVA. The correlation between mMRC score and routine spirometry measurements was examined using the non parametric Spearman rank correlation. Statistical significance was taken at $p \leq 0.05$.

RESULTS

Sitting, air

Table 1 shows the anthropometric characteristics and baseline lung function of the patients in the sitting position. FVC, FEV₁, expiratory reserve volume (ERV) and IC were reduced as compared to predicted values. In this posture none of the patients exhibited tidal EFL. Dyspnea at rest was modest, as indicated by the low value of the VAS score (12±2 mm). The significant correlation coefficients of mMRC vs the respiratory variables are shown in Table 2: mMRC correlated with IC (%pred), FVC (%pred) and FEV₁ (%pred) (P=0.006, 0.009 and 0.038, respectively), as well as with age (P=0.042) and V'O₂max (%pred) (P=0.001).

Supine, air

Shifting to the supine position caused the FVC to decrease (Δ FVC=-0.20±0.04 L; P<0.01) and, as expected, IC to increase (Δ IC=0.42±0.09 L; P<0.01), while the breathing pattern remained unchanged. In this position, eight patients (57%) became flow limited. These patients had lower ERV than the non flow limited patients (0.25±0.04 L vs 0.49±0.10 L, respectively, P=0.02) (Table 3 and Fig. 2). Dyspnea sensation tended to increase from sitting to supine position, but the increase was significant only in those patients who became flow limited (Δ VAS 7±1, P<0.01). Because of the occurrence of tidal EFL 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 had significantly lower FVC than non flow limited patients (71±6 vs 92±4 %pred, P=0.02, respectively) and a higher BMI than the latter (30±1 vs 25±1 kg m⁻², P<0.01, respectively). No difference was found in smoking history between the two groups of patients. In this regard, it is interesting that all the 3 non-smokers of this 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, nor changed inspiratory capacity (Fig. 3). Heliox caused a modest reduction of inspiratory time (Δ Ti=0.12±0.04 s, P<0.01) and dyspnea sensation (Δ VAS=1.4±0.04 s, P<0.01), independent of posture and flow limitation.

DISCUSSION

The new finding of this 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 a change in inspiratory capacity. Consequently in these patients tidal EFL arose from abnormalities within the peripheral part of the tracheobronchial tree, as it occurs in COPD patients at rest (5).

Patient population

Our patients exhibited a spirometric pattern compatible with restriction, since FVC, FEV₁, ERV and IC were reduced, whereas FEV₁/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).

Dyspnea sensation at rest (Table 1) in the sitting position was modest, as previously reported in stable CHF patients (2). Age and VO₂max were independent predictors of mMRC, the dependence on age could be related to the age-dependent impairment of the respiratory system (18). Because the mMRC scale measures the degree of breathlessness related to daily activities, it is not surprising that in our patients the best correlation of the mMRC score was with V'O₂max (Table 2). The mMRC score was also closely correlated 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 total lung capacity because of an increased volume of non pulmonary intrathoracic structures, as in CHF patients (17). One may speculate that in the latter case the volume of the chest wall could be even increased, depending on the combined effect of the volumetric increase of non pulmonary intrathoracic structures and the decrease of lung compliance. In CHF patients, the inspiratory muscles, therefore, would work in a condition of mechanical disadvantage, increasing the dyspnea 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 8 patients (57%) became flow limited when supine. One major factor involved in the development of tidal EFL in the supine position is the reduction of lung recoil secondary to the decrease of lung volume which occurs because of the expiratory action of the abdomen and shift of blood into the thoracic cavity. The changes in ERV occurring in our patients should closely reflect those in functional residual capacity, because changes in residual volume between the upright posture and recumbency are very small in normal subjects and residual 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 of maximal flows with decreasing lung volume is more prominent than in normal subjects: it has been shown in fact that maximal expiratory flows can be markedly reduced (65 %pred) in the lower 25% of FVC without any substantial fall of FEV₁ (92 %pred) (21). This could have occurred in our patients, because in the supine position flow limited patients had a lower ERV than non flow limited subjects (Table 3 and Fig. 2, *upper panel*), even when ERV was expressed in % of standing FVC (Fig. 2, *lower panel*). Moreover, our flow limited patients were overweight; this might have contributed to the decrease of ERV as shown by a significant correlation between BMI and ERV (P=0.03), thus favoring the occurrence of EFL. Mild obesity by itself, 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) we have found that only 3 exhibited EFL when supine, an incidence significantly lower than that of CHF patients (P<0.01). Moreover no EFL was observed in 9 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 6 patients who were non flow limited in 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 it is usually the case in CHF patients (2, 23). Heliox may 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 our 8 patients who were flow limited in the supine position heliox did not increase IC nor change the duration of expiration and the 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 of resistance or compliance or both. Unfortunately there is no information about the functional state of the peripheral airways in CHF patients. When respiratory resistance was investigated with the forced oscillation technique, an enhanced frequency dependence of respiratory resistance has been detected (20, 24), a finding which 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 resistances is normal (23) or moderately elevated (20, 24). In contrast, in the supine position, the increase of

respiratory resistance is always greater than normal (20, 23). This suggests that the increase of respiratory resistance is due to the decrease of lung volume which takes place on switching from sitting to supine and/or vascular engorgement and interstitial edema, all factors which should mainly affect peripheral airways. In this connection, it should be noted that the effect of vascular engorgement and interstitial edema on peripheral resistance depends on pulmonary volume. Indeed, Ishii et al. (26) found that in open-chest dogs the increase in peripheral airway resistance with vascular engorgement, interstitial and alveolar edema was markedly reduced and eventually abolished by increasing lung volume. It seems likely that in at least some of our supine patients vascular engorgement was increased. In fact it has been shown (27) that in about 50% of CHF patients pulmonary capillary wedge pressure increases when switching from sitting to supine. On the other hand, studies performed in animal models have provided contrasting results: vascular engorgement and interstitial edema resulted in a decreased small airway cross section and presumably increased pulmonary resistance when airway caliber was measured with high resolution computed tomography (28) but not when it was assessed on histologic preparations (29). Although vagally mediated bronchoconstriction might have also contributed to the increase of respiratory resistance in the supine position, it has been shown that administration of large doses of ipratropium, a muscarinic antagonist, to CHF patients attenuates the increase of pulmonary resistance only slightly (20).

While breathing heliox, there was a significant reduction of dyspnea 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 supine position, the functional alterations must occur at a peripheral level, because of the absence of density dependence.

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Legends for figures

Figure 1. Example of a non flow limited (panel A) and of a flow limited (panel B) CHF patient breathing air in supine position. *From top to bottom*: time course of flow, volume (measured in litres from TLC) and mouth pressure with (second breath) and without NEP application. The bottom panel shows the corresponding flow-volume curves.

Figure 2. *Top panel*: average expiratory reserve volume of 14 CHF patients breathing air sitting and supine stratified according to presence (n=8) or absence (n=6) of tidal EFL in supine position. All patients were not flow limited while sitting. *Lower panel*: as above, with the expiratory reserve volume expressed as % of FVC in sitting position.

Figure 3. *Top panel*: mean values of IC during air and heliox breathing in 14 supine CHF patients. Bars are half ranges. *Lower panel*: relationship between IC in heliox and in air in 14 supine CHF patients. Dotted line: identity line.

Table 1. Anthropometric and routine lung function data of seated CHF patients breathing air stratified according to presence or absence of tidal EFL in the supine position

	All		Flow limited		Non flow limited	
Subjects, No.	14		8		6	
Gender (M/F)	13/1		8/0		5/1	
Age, yr	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	1.9	± 0.3	2.3	± 0.3	1.3	± 0.4
VAS, mm	12	± 2	14	± 2	8	± 3
Smokers/Non smokers	11/3		5/3		6	
V'O₂max, mL kg⁻¹ min⁻¹	16.1	± 1.5	14.4	± 1.7	18.5	± 2.7
V'O₂max, %pred	56	± 4.6	51.7	± 5.4	62	± 7.6
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
FEV₁, %pred	72	± 4	63	± 4*	84	± 4
FEV₁/FVC, %pred	94	± 2	92	± 2	95	± 3
IC, %pred	73	± 5	66	± 6	81	± 6
ERV, %pred	80	± 10	65	± 12	100	± 14

Values are mean ± SE. BMI: body mass index; mMRC: modified Medical Research Council score; VAS: Visual Analog Dyspnea score; V'O₂max: maximal oxygen uptake; AT: anaerobic threshold; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; IC: inspiratory capacity; ERV: expiratory reserve volume.

*: significantly different from Non flow limited patients (P<0.05)

Table 2. Significant Spearman's correlation coefficients of mMRC to various anthropometric and respiratory parameters in seated CHF patients

	<i>mMRC</i>	
	<i>r_s</i>	<i>P Value</i>
Age, years	0.548	0.042
V'O₂max, %pred	-0.782	0.001
FVC, %pred	-0.665	0.009
FEV₁, %pred	-0.559	0.038
IC, %pred	-0.693	0.006

mMRC: modified Medical Research Council score; V'O₂max: maximal oxygen uptake; FVC: forced vital capacity; FEV₁: forced expiratory volume in one second; IC: inspiratory capacity.

Table 3. IC, ERV, VAS and breathing pattern during air and heliox breathing in the supine position in CHF patients stratified according to the presence or absence of tidal EFL

	Flow limited		Non flow limited	
	air	heliox	air	heliox
No	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
Ti, s	1.47 ± 0.13	1.37 ± 0.11 †	1.58 ± 0.16	1.49 ± 0.19 †
Te,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/Te, L/s	0.36 ± 0.03	0.38 ± 0.03	0.35 ± 0.05	0.36 ± 0.06
VAS, mm	21 ± 3	19 ± 2 †	11 ± 4	9 ± 3 †

Values are given as mean ± SE.

IC: inspiratory capacity; ERV: expiratory reserve volume; V_T: tidal volume; Ti: duration of inspiration; Te: duration of expiration; V_T/Te: mean expiratory flow; VAS: Visual Analog Dyspnea score.

*: significantly different from Non flow limited during air or heliox breathing (P<0.05)

†: significantly different from air (P<0.05)

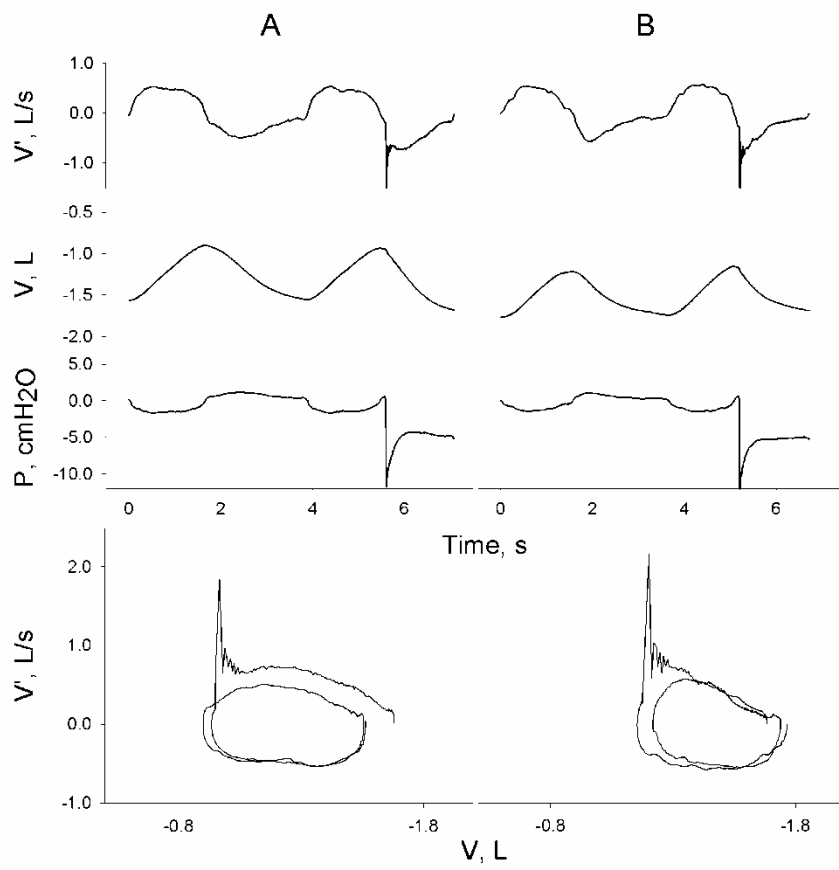


Figure 1

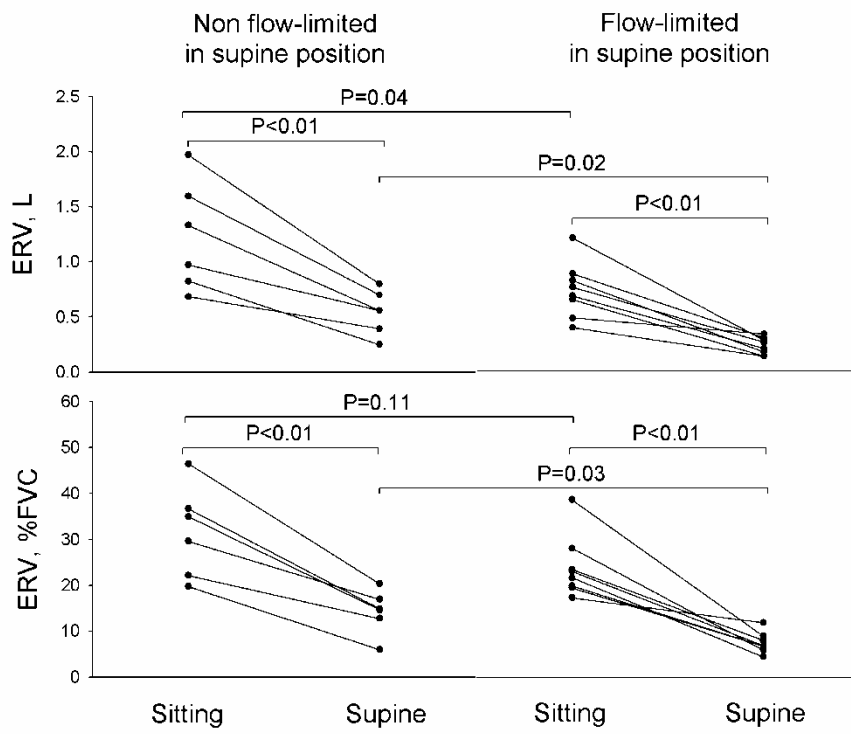


Figure 2

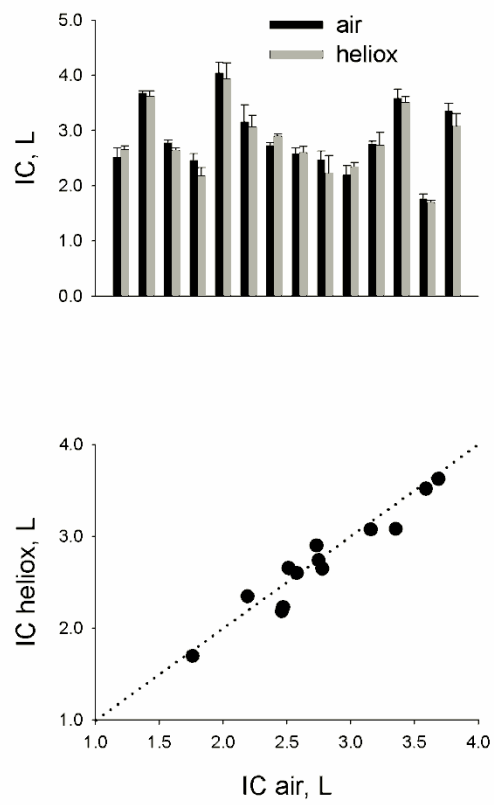


Figure 3