ERJ Express. Published on October 27, 2011 as doi: 10.1183/09031936.00125011

Title of manuscript: The resistive and elastic work of breathing during exercise in patients with chronic Heart Failure

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Abstract

Patients with Heart Failure (HF) display numerous derangements in ventilatory function, which together serve to increase the work of breathing (Wb) during exercise. However, the extent to which the resistive and elastic properties of the respiratory system contribute to the higher Wb in these patients is unknown.

We quantified the resistive and elastic Wb in patients with stable HF (n = 9, NYHA I-II) and healthy control subjects (n = 9) at standardised minute ventilations during graded exercise. Dynamic lung compliance was systematically lower for a given level of minute ventilation in HF patients than controls ($P < 0.05$). HF patients displayed slightly higher levels of inspiratory elastic Wb, with greater amounts of ventilatory constraint and resistive Wb than control subjects during exercise ($P < 0.05$).

Our data indicates that the higher Wb in HF patients is primarily due to a greater *resistive*- rather than *elastic*-load to breathing. The greater resistive Wb in these patients likely reflects an increased hysteresivity of the airways and lung tissues. The marginally higher inspiratory elastic Wb observed in HF patients appears related to a combined decrease in the compliances of the lungs and chest wall. The clinical and physiological implications of our findings are discussed.

Keywords: Heart Failure, Respiratory mechanics, Work of breathing

Introduction

The capacity to perform exercise is often severely reduced in patients with Heart Failure (HF) [1-3]. These patients typically display a blunted cardiac output response to exercise concomitant with derangements in ventilatory function, including: gas-exchange abnormalities, obstructive-restrictive lung disorders, decreased lung compliance, etc [4-7]. Accordingly, the energetic demands of exercise for HF patients may be compounded by an inordinately high work of breathing (Wb) for a given level of minute ventilation ($\dot{V}_E$) and external work [8-9]. This heightened Wb necessitates greater O_2 delivery to the respiratory muscles, potentially at the expense of O_2 supply to the locomotor muscles, impairing the patient's ability to perform muscular work [10-11]. Indeed, exercise capacity increases in these patients when the Wb is unloaded via assisted ventilation or by breathing reduced density gases [12-13]. It can then be reasoned that an elevated Wb contributes to the development of exertional fatigue in HF. Despite this rationale, there exists no systematic quantification of the Wb across the range of minute ventilations experienced by HF patients during dynamic exercise.

Pulmonary function in HF patients is typified by an overall restrictive lung disorder secondary to an increase in the elasticity of lung tissues, and/or a decreased ability to inflate the lungs due to an enlarged heart (i.e., cardiomegaly) [14-18]. In addition, there is cause to believe that resistance of the airways and lung tissues is greater in HF patients compared to healthy, age-matched individuals at rest, and during exercise [19-20]. Such ventilatory derangements in these patients would serve to increase the amount of respiratory muscle work required to achieve and maintain a given tidal volume (V_T) and respiratory frequency (f_R), thereby changing the pattern of breathing observed during exercise. Although many investigators appreciate that the *resistance* and *elastance* of the respiratory system are greater in this population, it is uncertain to what extent these parameters contribute to the overall higher Wb anticipated in these patients at a given level of $\dot{V}_E$ during exercise.

The aims of the present study were to quantify the resistive and elastic components of the Wb in patients with stable HF and healthy, age-matched individuals at standardised levels of $\dot{V}_E$ during graded exercise. It was hypothesised that HF patients would display greater amounts of resistive and elastic respiratory muscle work at each level of $\dot{V}_E$ than control subjects. Currently, there are no specific guidelines for the

management of respiratory symptoms in HF. The findings of this study may therefore aide in the improvement of existing treatment strategies for these patients, and/or indicate other therapeutic targets to consider in the clinical management of this population.

Materials and methods

Subjects and Ethical Approval. Nine patients with a history of HF, and nine healthy, age-matched control subjects volunteered to participate in the present study. The HF patients recruited for the study were required to meet the following criteria: (i) at least a 1-year history of known HF; (ii) New York Heart Association (NYHA) Class I, II or III symptoms; (iii) an ejection fraction ≤ 35% measured via echocardiography; (iv) no history of dangerous cardiac arrhythmias; (v) no pacemakers; (vi) at least one prior hospitalisation due to HF. All patients were receiving standard optimised pharmacotherapies for the management of HF at the time of the study. The age-matched control subjects were recruited from the surrounding community, and were current non-smokers (past 15 yr) with no history of cardiac or pulmonary diseases. Participants were excluded from the study if BMI ≥ 35 $kg \cdot m^2$ and/or reported a smoking history >15 pack-years. All participants provided written informed consent to participate in the study, which had been approved by the Institutional Review Board of the Mayo Clinic and Foundation. Each subject had been exposed to formal exercise testing on at least one prior occasion – all individuals were familiar with the exercise mode of cycle ergometry.

Graded exercise test. All subjects performed a graded exercise test to volitional exhaustion on an electronically-braked upright cycle ergometer (Lode Corival, Groningen, Netherlands). The graded exercise protocol commenced with 2 min of unloaded cycling, after which the power output was increased every 2 min by 20 W (for HF patients) or 30 W (for control subjects). A self-selected pedal cadence (60 – 70 $rev \cdot min^{-1}$) was maintained by each subject until exhaustion. Cardiac rhythm and heart rate were monitored continuously during the graded exercise test. Each individual reported an RPE score of 18 – 20 at volitional exhaustion. Pulmonary gas-exchanged was determined breath-by-breath via mass spectrometry (model 1100; Pelkin-Elmer, MA, USA) and a bi–directional differential pressure pneumotachograph (pre-Vent, Medical Graphics Corporation, St. Paul, MN, USA) while wearing a nose-clip. Peak values are reported as the average of the final 60 s of graded exercise.

Respiratory pressures. Oesophageal pressure (P_{OES}) was measured using a latex balloon-tip catheter (Ackrad Laboratories, CooperSurgical, Trumbull, CT, USA) that was inserted via the nose to approximately 45 cm distal to the nares. The balloon-tip catheter was inflated with 1 ml of air, and the "occlusion" test [21] was performed to ensure correct placement (i.e., lower one-third of the oesophagus). Mouth pressure (P_{MO}) was sampled via a lateral port in the mouthpiece. The catheters were connected to differential pressure transducers (MP45, Validyne Corporation, Northridge, CA, USA) which were calibrated using a water manometer before each test.

Respiratory mechanics. Before and immediately after the graded exercise test, subjects performed 7 to 10 vital capacity manoeuvres with varying degrees of effort (i.e., 20% through 100% of maximal effort). These efforts defined the maximal inspiratory and expiratory flow-volume envelopes for each subject, with minimal artefact due to thoracic-gas compression [22]. Subjects were also instructed to perform maximal inspiratory manoeuvres to determine inspiratory capacity (IC) while at rest, and 2-3 times towards the end of each minute during graded exercise. All pulmonary function tests were performed while seated on the cycle ergometer. The methods used to estimate maximal ventilatory capacity (MVC) were modified from those described by others [23-24]. The degree of expiratory flow-limitation during exercise was assessed by comparing the subject's exercise tidal flow-volume loop to their maximal volitional flow-volume envelope, and by determining the subject's maximal effective expiratory pressures using the isovolume pressure-flow technique [25]. Static recoil pressure of the chest wall was measured before graded exercise using the quasi-static relaxation technique [26]. The components of the work of breathing were quantified using modified Campbell diagrams constructed from flow, pressure and volume data obtained during graded exercise [27]. The reader is directed to the online data supplement for a detailed description of the above methodological procedures.

Data analysis. The analog signals of the mass spectrometer, pneumotachograph, P_{MO} and P_{OES} were digitised at 100 Hz (PCI-DAS6034, Measurement Computing Corporation, Norton, MA, USA), and subsequently analysed with custom-written software to provide breath-by-breath indices of pulmonary gas-exchange and respiratory mechanics. All indices of respiratory mechanics were averaged into bins corresponding to minute ventilations of 20, 40, 60, and 80 $L \cdot min^{-1}$.

Statistical analyses. The subject characteristics, pulmonary function, and peak exercise data were compared between groups using unpaired *t*-tests. The differences between groups for all measures of respiratory mechanics at standardised minute ventilations during graded exercise were evaluated using a two-way mixed factor analyses of variance (ANOVA). Given that obesity (specifically, visceral fat-mass) is known to influence respiratory mechanics during exercise [28], subjects' body mass was entered into the ANOVA model as a covariate. For the majority of parameters, body mass was not a significant covariate. When body mass was identified as a significant covariate in the ANOVA model, it did not change the overall differences observed between groups for the corresponding parameter. Statistical analyses were considered significant if $P < 0.05$. All values are reported as means ± standard error of the mean (SEM).

Results

Subject characteristics and peak exercise data. Two HF patients were NYHA Class I, and the remaining patients ($n = 7$) were NYHA Class II. The mean ejection fraction of HF group was 32 ± 1%. The HF patients were taking a combination of angiotensin converting enzyme inhibitors ($n = 9$), diuretics ($n = 6$), anti-arrhythmic agents ($n = 4$), statins ($n = 6$), non-selective adrenergic receptor blockers ($n = 8$), and β_1-adrenergic receptor blockers ($n = 2$). None of the control subjects were taking prescription medications for cardiovascular, metabolic or pulmonary diseases at the time of the study.

The subjects' physical characteristics, pulmonary function, and peak exercise values are presented in Table 1. Two healthy, control subjects and four HF patients reported a positive smoking history – all other participants reported no smoking history. There were no group differences for age and height, although body mass and body mass index (BMI) were significantly greater for patients with HF than control subjects ($P < 0.05$). HF patients exhibited significantly lower values for FVC, FEV_1, FEV_1/FVC, PEFR, and $FEF_{25\%-75\%}$ when compared to control subjects ($P < 0.05$). However, the predicted values for the above parameters in HF patients were, on average, toward the lower end of the normal range. Nevertheless, these results indicate a greater degree of lung restriction and airway obstruction in HF patients relative to the healthy, age-matched individuals of the present study. While resting inspiratory capacity was not different between groups, EELV at rest was significantly lower in patients with HF compared to the control group ($P < 0.05$). The chest wall compliance of HF patients (150 ± 30 ml·cmH_2O^{-1}, 99 ± 6% pred.) was significantly lower when compared to

control subjects (182 ± 38 ml·cmH_2O^{-1}, 109 ± 6% pred.) ($P < 0.05$). On average, peak O_2 uptake, work rate, $\dot{V}_E$ and heart rate were significantly lower for patients with HF compared to healthy control subjects ($P < 0.05$) and predicted scores.

Respiratory mechanics. The pattern of breathing during graded exercise for HF patients and control subjects are reported in Table 2. In comparison with control subjects, patients with HF demonstrated a more pronounced tachypnoea, evidenced by the smaller tidal volumes and faster respiratory frequencies toward higher levels of $\dot{V}_E$ ($P < 0.05$). The higher f_R values observed in HF patients were primarily due to significantly shorter inspiratory times compared to control subjects ($P < 0.05$). Mean inspiratory flows were not different between groups during graded exercise. However, mean expiratory flows for HF patients were marginally slower than those of control subjects at minute ventilations of 40 and 60 L·min^{-1} ($P < 0.05$).

The progression of ventilatory constraint during graded exercise in HF patients and control subjects is illustrated in Figure 1. At each level of $\dot{V}_E$, HF patients exhibited a greater degree of expiratory flow-limitation, and their exercise flow-volume loops occupied a greater proportion of maximal achievable flow rates (i.e., MVC), compared to the control subjects ($P < 0.05$). Dynamic lung volumes obtained during graded exercise are presented in Figure 2. The dynamic lung volumes of HF patients were systematically lower compared to control subjects at each level of $\dot{V}_E$ ($P < 0.05$). For the control group, EELV was significantly higher than resting values (i.e., dynamic hyperinflation) at levels of $\dot{V}_E$ greater than 60 L·min^{-1} ($P < 0.05$). Mean values for EELV of HF patients were systematically higher than resting values throughout graded exercise ($P < 0.05$). Dynamic lung compliance was significantly lower in HF patients at levels of $\dot{V}_E$ corresponding to 20, 40 and 60 L·min^{-1}. There appeared an appreciable, albeit non-significant, difference in dynamic lung compliance between HF patients and control subjects at a $\dot{V}_E$ of 80 L·min^{-1} (264 ± 26 mL·cmH_2O^{-1} v 333 ± 43 mL·cmH_2O^{-1}, $P = 0.09$).

The relationships between the total Wb and $\dot{V}_E$ during graded exercise are displayed in Figure 3. The total Wb was higher at level of $\dot{V}_E$ for patients with HF compared to control subjects during graded exercise ($P < 0.05$). The resistive and elastic components of the Wb during graded exercise are shown in Figure 4. In general, the inspiratory and expiratory resistive Wb was systematically higher in patients with HF compared

to control subjects at each level of $\dot{V}_E$ investigated ($P < 0.05$). Inspiratory elastic Wb was significantly higher for HF patients than control subjects at minute ventilations of 40 and 60 $L \cdot min^{-1}$ ($P < 0.05$). There were no consistent differences between groups for the expiratory elastic work at each level of $\dot{V}_E$ ($P > 0.30$).

Discussion

The major findings of the present study were that patients with stable HF are faced with an inordinately higher Wb compared to healthy, age-matched subjects for a given level of given $\dot{V}_E$. Furthermore, the overall higher mechanical cost of breathing in these patients appears due to greater amounts of *resistive* rather than *elastic* respiratory muscle work. The greater resistive Wb in HF patients most likely reflects an increase in airways and lung tissue resistance. On the other hand, the marginally higher inspiratory elastic Wb observed in these patients was related to a combined decrease in the compliances of the lungs and chest wall.

The work of breathing in heart failure. In 1934, Christie and Meakins [29] were the first to provide direct evidence that patients with congestive heart failure often present with an impaired distensibility of the lungs (i.e., dynamic lung compliance; $C_{L,dyn}$). Since then, other ventilatory derangements have been described in this population ranging from restrictive-obstructive disorders in pulmonary function, functional weakness of the respiratory muscles, and the development of severe ventilatory constraint during physical activity [14, 30-34]. These pathologies would together serve to increase the amount of work performed by the respiratory muscles per breath. Many investigators have provided support for this rationale using surrogate measures of the Wb, such as the pressure- and tension-time indices of oesophageal and diaphragmatic pressure traces, during exercise in patients with HF [30, 35-36]. It should be noted that these parameters are not indicative of respiratory muscle work *per se*, but rather provide an index of respiratory muscle blood flow and O_2 uptake [37-38]. Others have determined the Wb in HF patients using P_{OES}-V_T loops obtained during exercise [8-9, 11, 39]. However, these studies often neglected the elastic work incurred by movement of the chest wall, and may have therefore underestimated the total Wb in these patients. In the present study, we used the modified Campbell diagram to better quantify the overall Wb during exercise [27]. Figure 5 displays representative data from a HF patient and a healthy, age-matched control subject at a standardised $\dot{V}_E$ of ~80 $L \cdot min^{-1}$. It can be noted that all components of the Wb were appreciably greater for the HF patient compared to the

control subject – excepting the elastic work of expiration. These observations were characteristic of all HF patients over the range of minute ventilations investigated (Figure 4). Importantly, the systematically higher overall mechanical cost of breathing in HF patients appeared due to factors mediating an increase in the *resistive* rather than *elastic* Wb during graded exercise (Figure 6).

Resistive work of breathing. In agreement with previous observations [20, 31-32, 34], the HF patients of the present study displayed relatively greater airways obstruction compared to the healthy control subjects (Table 1). Hence, there appeared less reserve for HF patients to increase tidal flows before encroaching upon the mechanical constraints of the lungs during graded exercise (i.e., expiratory flow-limitation). Dynamic lung volumes were also lower, positioning the HF patient's tidal breath over a range of lung volumes where maximal achievable expiratory flows are further reduced. Consequently, these patients displayed a greater degree of expiratory flow-limitation, yielding slightly lower mean expiratory flows than control subjects at each level of $\dot{V}_E$. Therefore, much of the greater *expiratory* resistive Wb observed in HF patients appears related to the generation of expiratory pressures far in excess of those required to produce maximal flows [40]. The *inspiratory* resistive Wb was also higher in HF patients compared with control subjects during graded exercise. However, this greater inspiratory resistive Wb was not accompanied by higher mean inspiratory flows, where faster flow rates would have caused a rise in dissipative pressure losses during inspiration. Instead, it is likely that inspiratory resistive Wb was greater in HF patients due to an increased pulmonary resistance. We interpret the above findings to represent an increased *inspiratory* and *expiratory* resistive-load to breathing in HF patients during physical activity. Such an increased resistive-load to breathing in HF patients may arise from the development (or progressive worsening) of pulmonary congestion and/or an increased bronchomotor tone during graded exercise [8, 41-42].

It can be reasoned that left systolic dysfunction leads to an increase in pulmonary capillary pressures, facilitating the transudation of fluid into the pulmonary interstitium [5, 43]. Pulmonary congestion is thought to increase airways resistance by reducing luminal diameter due to bronchial or pulmonary vessel engorgement, and/or by causing an imbalance of interfacial and radial forces acting on the airway wall itself [44-46]. Additionally, a rise in extra-luminal pressure secondary to pulmonary congestion may promote the dynamic closure of dependent airways at relatively lower transmural pressures for any given lung volume during expiration (i.e., the Starling-resistor model) – although this enhanced airway collapsibility would

seemingly be offset by an increased bronchomotor tone. Indeed, there is cause to believe that pulmonary interstitial oedema leads to the development of airway hyperresponsivity in HF patients ('cardiac asthma') [46-47]. An increased bronchomotor tone during exercise may promote 'buckling' of the airway mucosa (particularly during expiration), and would certainly increase the resistance of the airways during spontaneous breathing. It should be noted that our measurement of the resistive Wb included the pressures lost to hysteresivity of the lung tissue itself. Importantly, the resistance of lung *tissue* increases when the pulmonary interstitium becomes oedematous, and during instances of increased bronchomotor tone [48-50]. It is therefore reasonable to suggest that pulmonary congestion, either through primary or secondary influences, may lead to an increase in both airways and tissue resistance of the lungs, thereby increasing the resistive-load to breathing in patients with HF during exercise.

Elastic work of breathing. Overall, HF patients displayed a more rapid-shallow breathing pattern for any given level $\dot{V}_E$ than control subjects. This 'exercise tachypnoea' is a hallmark of the disease, and appears inversely related to the dynamic compliance of the lungs during exercise [14]. Our data are consistent with these observations in that V_T and dynamic lung compliance were systematically lower, and f_R higher, in HF patients than control subjects during graded exercise (Table 2 and Figure 1). It can be reasoned that patients with HF adopt a rapid-shallow breathing pattern, at relatively lower operational lung volumes, to avoid a high elastic Wb due to increased lung 'stiffness'. In spite of these efforts, the lower compliances of the lungs and chest wall in these patients produced a higher *inspiratory* elastic Wb compared to control subjects during exercise (Figure 4 and 5) – the *expiratory* elastic work of breathing was negligible in both groups.

The reduction in dynamic lung compliance observed in HF patients may be attributed to a number of mechanisms: the competition between lung and cardiac tissue for intra-thoracic space (e.g., cardiomegaly); the erectile nature of an engorged pulmonary and/or bronchial vasculature; the development of pulmonary interstitial oedema, particularly during exercise; and remodelling of the lung parenchyma due to elevated circulating cytokines and/or chronic hydrostatic insult [18, 41, 51-53]. Although the mechanisms for the lower dynamic lung compliance have been well-described in HF, we also noted that compliance of the chest wall in these patients was lower (~18%) than control subjects. To the best of our knowledge, the later observation has not been reported in unaesthetised patients with stable HF. The reasons for such increased 'stiffness' of the chest wall in this population are unclear. Evidence suggests that subject anthropometric

characteristics do not adequately explain the differences in the compliance of the chest wall between individuals [54-55]. Thus, it is unlikely that chest wall compliance was lower in the HF group due to the larger body mass and BMI of the patients. In addition, we controlled for the age-related decline in chest wall compliance [55] by comparing HF patients to healthy, age-matched individuals. At present, the precise mechanisms which cause the decline in chest wall compliance in patients with stable HF require further investigation.

Interrelationships between resistive and elastic Wb. We caution the reader that although each component of the Wb has been treated separately in this discussion, we do not imply any degree of isolation between parameters. The mechanisms which affect an increase in the resistive Wb are likely to influence the elastic Wb, and *vice versa*. As mentioned above, continued pulmonary congestion may lead to airway hyperresponsiveness in patients with HF [46-47]. Bronchomotor tone not only regulates airways and lung tissue resistance, but also determines the dynamic elastance of the bronchial tree [56-57]. For example, when the smooth muscle layer of the airways contract, tension develops in the radial and longitudinal axes of the bronchial tree – this tension increases the amount of respiratory muscle force required to expand the dimensions of the lungs along these planes during inspiration. Indeed, recent evidence suggests that relaxation of airway smooth muscle via inhalation of short-acting bronchodilators decreases both pulmonary resistance and elastance in patients with HF [19]. Thus, with respect to our data, an increased bronchomotor tone may have therefore contributed to the decreased $C_{L,dyn}$ observed in HF patients during graded exercise.

Implications and clinical significance. The heightened Wb observed in HF patients necessitates greater O_2 delivery to the respiratory muscles during exercise – clearly an issue for patients with an already reduced cardiac reserve. The respiratory muscles may therefore compete with locomotor muscles for cardiac output during physical activity, thereby impairing the ability of these patients to perform the activities of daily living. Indeed, O_2 delivery to the locomotor muscles increases, and tolerance to physical activity improves, when the Wb is unloaded in HF patients during submaximal exercise [11-13, 58]. These findings, in conjunction with the observations of the present study, emphasise the importance of targeting respiratory symptoms in the management of patients with HF.

Methodological considerations. We used the modified Campbell diagram to quantify the resistive and elastic components of the Wb during exercise. Although this approach has been used widely in the past [59-61], the technique is not without its limitations. Our measurements of the total Wb did not include the additional mechanical cost incurred by deformation of the chest wall, hysteresivity of chest wall tissues, eccentric (negative) and/or isometric work performed by the respiratory muscles, compression of thoracic gas, and the work done on the abdominal viscera [60, 62]. The modified Campbell diagram may have therefore underestimated the 'true' mechanical cost of breathing in our subjects. It should be remembered that chest wall compliance was lower, and the degree of expiratory flow-limitation during exercise was higher, for HF patients than control subjects. Accordingly, the amount of respiratory muscle work lost to the hysteresivity and deformation of the chest wall, and that lost to thoracic gas compression, would be necessarily higher in patients with HF. If these sources of respiratory muscle work were accounted for in the present study, the differences in the Wb observed between groups would most likely be accentuated, rather than diminished.

The HF patients of the present study were, on average, heavier than control subjects (Table 1). Although it is reasonable to suggest that obesity may have contributed to the differences in respiratory variables between groups (i.e., HF v controls), entering participants' mass as a covariate into the analyses of variances performed in this study did not alter the significance of our findings; i.e., our observations cannot be adequately explained by differences in subject anthropometric characteristics between groups. It is worth noting, however, that there were a greater number of ex-smokers among HF patients than healthy, age-matched control subjects (4/9 patients v 2/9 controls). Smoking history was also relatively greater in HF patients than control subjects – although this comparison was not significant. It is possible that smoking-related decrements in airway calibre may have accounted for some of the obstructive changes observed in the patients with HF [34].

Conclusions. We report that the total Wb is systematically higher in HF patients than control subjects at standardised minute ventilations during physical activity. Importantly, we have shown that the inordinately higher Wb in HF patients is primarily due to a greater *resistive*-load to breathing. Specifically, HF patients adopt a rapid-shallow breathing pattern at relatively low lung volumes in an effort to avoid high levels of inspiratory elastic Wb. This breathing strategy comes at the expense of greater ventilatory constraint, expiratory flow-limitation, and therefore an increased expiratory resistive Wb. The reasons for the higher

inspiratory resistive Wb in HF patients are uncertain, but may involve an increase in both airways and tissue resistance of the lungs secondary to the development (or worsening) of pulmonary congestion, and/or increased bronchomotor tone during exercise. The mechanisms responsible for the relatively lower compliance of the chest wall in HF patients remain unclear. Overall, the ventilatory derangements observed in patients with HF affect an increase in the mechanical (and therefore O_2) cost of breathing at any given $\dot{V}_E$ when compared to healthy, age-matched control subjects during exercise. These findings contribute to the growing impetus for research examining the respiratory complications associated with HF.

Funding

This work was supported by the National Institute of Health [HL 71478 to B.D.J.].

Acknowledgements

The Authors of the present study would like to thank K. O'Malley, M. Hulsebus and A. Miller for their assistance in subject recruitment and data collection.

Conflict of Interest

The Authors have no conflicts of interest to declare.

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Table 1. Subject characteristics, pulmonary function, and peak exercise values in patients with heart failure (HF) and healthy control subjects.

	Control		HF	
	Measured	% predicted	Measured	% predicted
Age (yr)	55 ± 4		57 ± 4	
Height (cm)	179 ± 2		180 ± 2	
Body mass (kg)	86.4 ± 2.4		103.8 ± 4.1*	
BMI ($kg \cdot m^{-2}$)	26.4 ± 0.9		32.3 ± 0.9*	
Aetiology	--		4 IDC / 5 CAD	
Smoking History (pk. yrs)	1.9 ± 1.7		9.8 ± 5.5	
Pulmonary Function				
FVC (L)	5.12 ± 0.35	106 ± 3	4.34 ± 0.28*	92 ± 5*
FEV_1 (L)	4.27 ± 0.30	112 ± 3	3.31 ± 0.32*	90 ± 8*
FEV_1/FVC (%)	83.2 ± 1.6		74.8 ± 4.3*	
PEFR ($L \cdot sec^{-1}$)	9.95 ± 0.43	94 ± 3	7.90 ± 0.79*	76 ± 7*
$FEF_{25\%-75\%}$ ($L \cdot sec^{-1}$)	6.12 ± 0.29	127 ± 4	4.39 ± 0.52*	93 ± 10*
IC (L)	4.21 ± 0.24	107 ± 4	4.00 ± 0.33	92 ± 7
EELV (L)	0.91 ± 0.22		0.34 ± 0.09*	
Peak exercise				
$\dot{V}O_{2peak}$ ($L \cdot min^{-1}$)	2.87 ± 0.34	100 ± 14	1.79 ± 0.16*	53 ± 7*
Peak power (W)	228 ± 30		127 ± 10*	
HR_{peak} ($beats \cdot min^{-1}$)	156 ± 9	94 ± 4	106 ± 6*	68 ± 3*
$\dot{V}_{Epeak}$ ($L \cdot min^{-1}$)	146.0 ± 16.0		80 ± 4.7*	
$Wb_{TOTpeak}$ ($J \cdot min^{-1}$)	485 ± 107		190 ± 9*	

Values represent mean ± SEM. BMI: body mass index; IDC: idiopathic dilated cardiomyopathy; CAD: coronary artery disease; pk. yrs: pack years; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; PEFR: peak expiratory flow rate; $FEF_{25\%-75\%}$: mid-expiratory flow rate; IC: inspiratory capacity; EELV: end-inspiratory lung volume; $\dot{V}O_{2peak}$: peak O_2 uptake; $\dot{V}_{Epeak}$: peak minute ventilation; $Wb_{TOTpeak}$: total work of breathing observed at peak exercise. *Significantly different from control group, $P < 0.05$.

Table 2. Timing and pattern of breathing during graded exercise in patients with heart failure (HF) and control subjects.

	20 L·min^{-1}		40 L·min^{-1}		60 L·min^{-1}		80 L·min^{-1}	
	Control	HF	Control	HF	Control	HF	Control	HF
V_T (L)	1.07 ± 0.04	1.03 ± 0.06	1.73 ± 0.05	1.59 ± 0.07*	2.27 ± 0.05	2.02 ± 0.11*	2.63 ± 0.10	2.19 ± 0.16*
f_R (breaths·min^{-1})	20.8 ± 0.9	21.9 ± 1.2	23.4 ± 0.7	25.5 ± 1*	27.0 ± 0.9	30.0 ± 1.4*	30.8 ± 1.3	34.9 ± 1.9*
T_I (s)	1.27 ± 0.08	1.12 ± 0.08	1.20 ± 0.06	1.03 ± 0.05*	1.06 ± 0.05	0.90 ± 0.06*	0.94 ± 0.05	0.79 ± 0.05*
T_E (s)	1.75 ± 0.09	1.76 ± 0.13	1.42 ± 0.03	1.39 ± 0.06	1.21 ± 0.03	1.15 ± 0.04	1.04 ± 0.04	0.90 ± 0.06*
T_I/T_{TOT}	0.42 ± 0.01	0.40 ± 0.01	0.46 ± 0.01	0.43 ± 0.01*	0.47 ± 0.01	0.44 ± 0.01*	0.47 ± 0.01	0.47 ± 0.01
V_T/T_I (L·sec^{-1})	0.85 ± 0.03	0.93 ± 0.03	1.46 ± 0.04	1.54 ± 0.03	2.17 ± 2.26	2.26 ± 0.03	2.82 ± 0.06	2.73 ± 0.12
V_T/T_E (L·sec^{-1})	0.62 ± 0.02	0.59 ± 0.02	1.22 ± 0.02	1.14 ± 0.02*	1.89 ± 0.03	1.75 ± 0.04*	2.52 ± 0.04	2.47 ± 0.15

Values represent mean ± SEM. V_T: tidal volume; f_R; respiratory frequency; T_I: inspiratory duration; T_E: expiratory duration; T_I/T_{TOT}: inspiratory duty-cycle. *Significantly different from control group, $P < 0.05$.

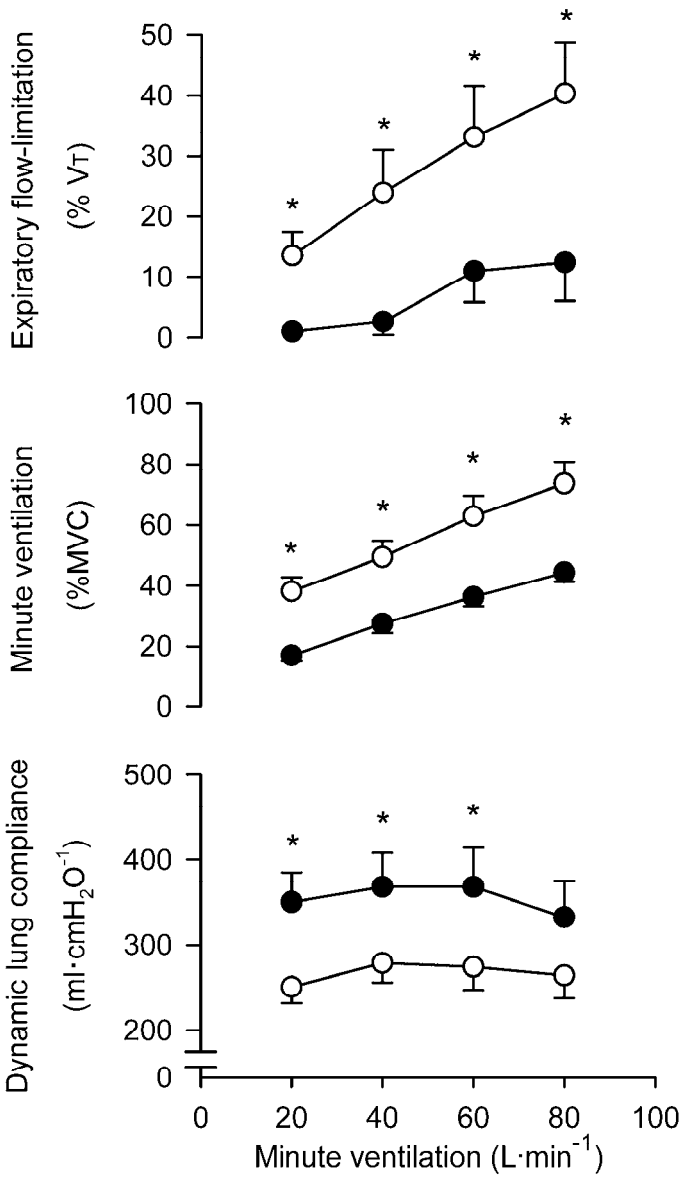

Figure 1. Ventilatory constraint during graded exercise in patients with heart failure (○) and healthy control subjects (●). Values represent mean ± SEM. VT: tidal volume; MVC: maximal ventilatory capacity. *Significantly different between groups, $P < 0.05$. Note: there appeared a trend towards significance for dynamic lung compliance between heart failure patients and control subjects at a minute ventilation of 80 $L \cdot min^{-1}$, $P = 0.09$.

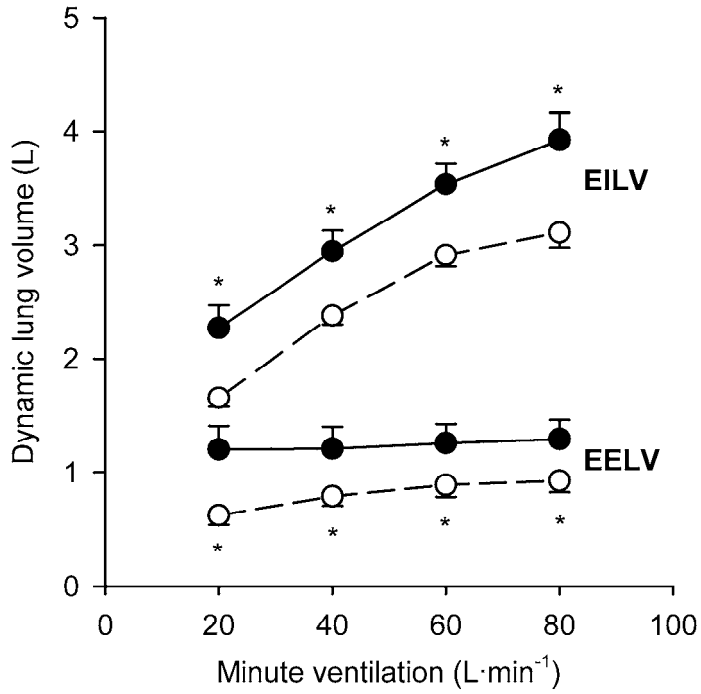

Figure 2. Dynamic lung volumes during graded exercise in patients with heart failure (○) and healthy control subjects (●). Values represent mean ± SEM. EILV: end-inspiratory lung volume; EELV: end-expiratory lung volume. *Significantly different between groups, $P < 0.05$. Note: the dynamic lung volumes of patients with chronic heart failure were systematically lower during the graded exercise test compared to the control group.

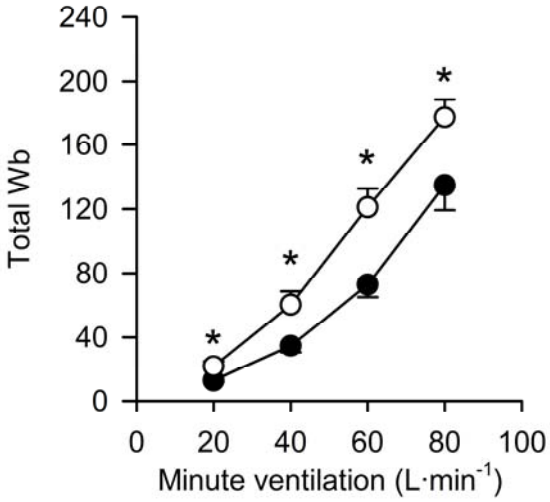

Figure 3. Total work of breathing (Wb) v. minute ventilation during graded exercise in patients with heart failure (○) and healthy control subjects (●). Values represent mean ± SEM. *Significantly different between groups, $P < 0.05$. Wb: work of breathing in joules per minute ($J \cdot min^{-1}$).

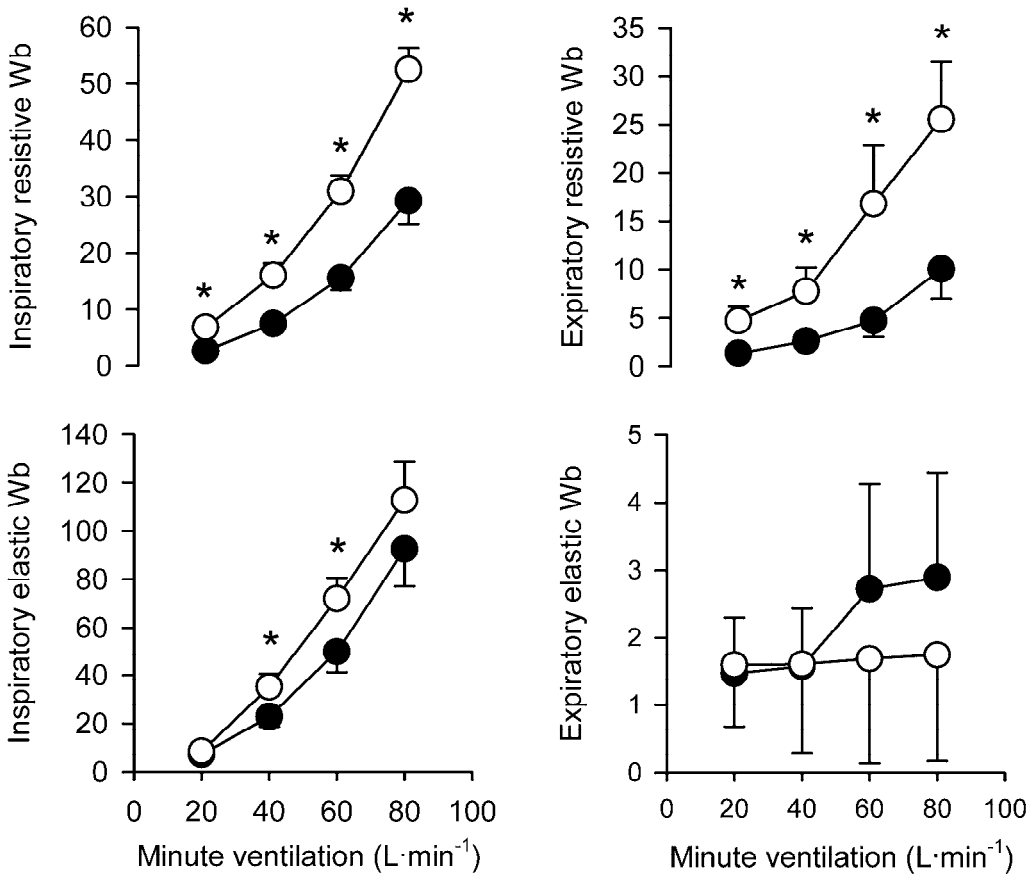

Figure 4. Resistive and elastic work of breathing v. minute ventilation during graded exercise in patients with heart failure (○) and healthy control subjects (●). Values represent mean ± SEM. Wb: work of breathing in joules per minute ($J \cdot min^{-1}$). *Significantly different between groups, $P < 0.05$.

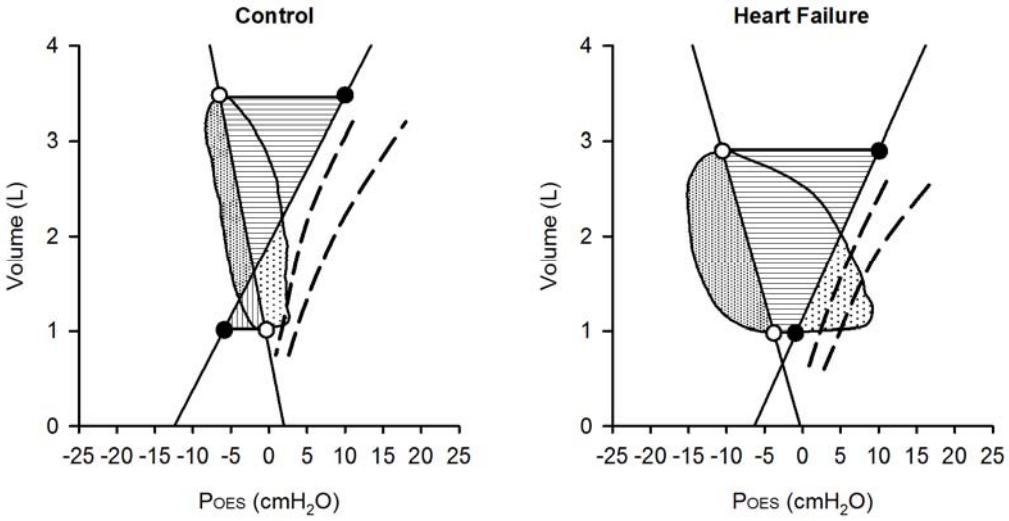

Figure 5. The resistive and elastic work of breathing (Wb) in a representative control subject, and a patient with heart failure (HF) at similar minute ventilations. This figure displays representative data from a healthy control subject (71 yr; 78.0 kg; $\dot{V}_E$ = 80.5 L·min^{-1}) and a patient with HF (NYHA II; EF = 25%; 73 yr; 96.4 kg; $\dot{V}_E$ = 80.4 L·min^{-1}) during graded exercise. The open circles represent pressure points of zero-flow during the tidal breath. The slope of the intersecting line between open circles equals the dynamic lung compliance. The closed circles denote recoil pressures of the chest wall at points of zero-flow during the tidal breath. Fine stippling (▩) represents inspiratory resistive Wb. Coarse stippling (⬚) denotes expiratory resistive Wb. The horizontal hatching (▤) represents inspiratory elastic Wb, whereas vertical hatching (▥) denotes expiratory elastic Wb. The dashed lines demarcate the range of maximum effective expiratory pressures.

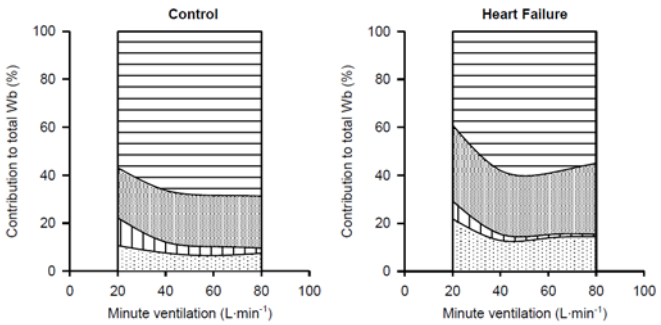

Figure 6. The relative contributions of resistive and elastic respiratory work to the total work of breathing (Wb) during graded exercise. The left and right panels illustrate the general relationship between each component of the work of breathing and minute ventilation during graded exercise for patients with heart failure (HF) and healthy control subjects, respectively. Fine stippling (▩) represents inspiratory resistive Wb. Coarse stippling (▩) denotes expiratory resistive Wb. The horizontal hatching (▤) represents inspiratory elastic Wb, whereas vertical hatching (▥) denotes expiratory elastic Wb. Note: the relative contribution of inspiratory and expiratory resistive Wb to the total mechanical cost of breathing appears larger for HF patients than control subjects during graded exercise.