Inspiratory Muscle Relaxation Rate Slows during Exhaustive Treadmill Walking in Patients with Chronic Heart Failure

PHILIP D. HUGHES, NICHOLAS HART, CARL-HUGO HAMNEGÅRD, MALCOLM GREEN, ANDREW J. S. COATS, JOHN MOXHAM, and MICHAEL I. POLKEY

Respiratory Muscle Laboratory and Department of Cardiology, Royal Brompton Hospital and National Heart and Lung Institute, Imperial College School of Medicine; Respiratory Muscle Laboratory, Denmark Hill Campus, Guy's, King's and St Thomas's School of Medicine, London, United Kingdom; and Department of Pulmonary Medicine, Sahlgrenska University Hospital, Göteborg, Sweden

Exercise intolerance is a feature of chronic heart failure (CHF). We hypothesized that excessive loading of the respiratory muscle pump might contribute to exertional breathlessness. One marker of excessive muscle-loading is slowing of maximum relaxation rate (MRR) and, therefore, to test our hypothesis, we investigated the effect of exhaustive treadmill walking on inspiratory muscle MRR in patients with CHF. We studied eight stable patients with mild-moderate CHF walking on a treadmill until termination because of severe dyspnea. Inspiratory muscle MRR was determined from esophageal pressure (Pes) change during submaximal sniffs (Sn) before and immediately after exercise to a mean (SD) minute ventilation of 77 (18) L/min. For comparison, nine healthy subjects performed a similar protocol; exercise was terminated either by severe dyspnea or when minute ventilation reached 100 L/min. There were no significant differences in terms of heart rate, respiratory rate, tidal volume, or inspiratory duty cycle at cessation of exercise. The mean slowing of Sn Pes MRR in the first minute after termination of exercise in the CHF group was 22.4% and in the normal control group it was 2.8% ($p < 0.01$). Our data show that slowing of inspiratory muscle relaxation rate occurs in patients with CHF walking to severe breathlessness. We conclude that severe loading of the inspiratory muscles is a feature of exertional dyspnea in CHF.

In chronic heart failure (CHF) a combination of disuse, underperfusion, and neurohormonal mechanisms lead to reduced peripheral muscle strength and endurance (1, 2). Although these changes may explain limb fatigue during exercise in CHF, it is less clear if exertional dyspnea can be attributed to similar mechanisms affecting the respiratory muscles. Although it is known that pulmonary compliance is reduced in CHF (3, 4), increasing the work of breathing, we have recently shown using detailed tests (5) that respiratory muscle strength is largely preserved in CHF. However, other observations suggest that an imbalance between the load applied to and the capacity of the inspiratory muscle pump could contribute to exercise-induced dyspnea in CHF. In particular it has been observed that exercise capacity can be extended if the work of breathing is reduced using a helium-oxygen mixture (6) or inspiratory pressure support (7). However, direct evidence supporting this hypothesis is currently lacking.

When skeletal muscle operates under conditions of excessive load the maximum rate of relaxation slows; this property, which is an active process, can be determined for the inspiratory muscles from the esophageal pressure trace after a voluntary sniff (Sn Pes) (8, 9). We have previously shown that this method can detect changes in the maximum relaxation rate (MRR) of inspiratory (8) muscle in normal subjects after hyperventilation and in patients with chronic obstructive pulmonary disease (COPD) after exhaustive treadmill walking (10).

In the present study we used measurement of MRR to test the hypothesis that exercise in CHF results in excessive loading of the inspiratory muscles; we therefore measured sniff esophageal pressure maximum relaxation rate (Sn Pes MRR) in patients with CHF walking to exhaustion on a treadmill. Our rationale was that slowing of Sn Pes MRR would support this hypothesis and suggest a possible contribution to the etiology of breathlessness in CHF.

METHODS

Subjects

The age and lung function of the subjects, together with New York Heart Association (NYHA) status and cardiac ejection fraction measured by nuclear angiography for the CHF patients are presented in Table E1 in the online repository. Although the control subjects were younger (mean difference, 9.8 yr; $p = 0.18$; 95% CI, −5.1 to +24.7 yr) this difference did not achieve statistical significance. Both FEV_1 and VC were reduced in patients with CHF ($p = 0.006$ and $p = 0.009$, respectively, but there was no difference between the two groups with regard to their global maximum inspiratory muscle strength as determined by Sn Pes_{max}. Eight stable male patients with CHF were studied, in three the cause of heart failure was dilated cardiomyopathy and in the remaining five it was ischemic heart disease. None of the patients was an active smoker and none had symptoms to suggest chronic lung disease, although one patient had undergone a lobectomy for tuberculosis 40 yr previously. Patients were selected if they had previous experience of walking on a treadmill and could do so without developing angina, dysrhythmias, or severe leg fatigue. For comparison, nine healthy control subjects were studied. All were familiar with physiological experiments, including measurements of respiratory muscle strength; in the case of the elderly control subjects this was because of previous participation in another study (11). The study was approved by the hospital ethics review committee, and all subjects gave written informed consent.

Equipment

Spirometry was performed using a wedge bellows spirometer (Vitalograph, Bucks, UK) and lung volumes were measured using a whole-body plethysmograph (Jaeger, Würzburg, Germany). Predicted values were taken from the European Respiratory Society guidelines (12).

Esophageal pressure (Pes) was measured using a 10-cm latex balloon attached to a 110-cm plastic catheter and inflated with 0.5 ml air. Gastric pressure (Pga) was measured using a similar balloon catheter inflated with 2 ml air. The two balloon catheters were introduced pernasally and positioned in the esophagus and stomach in the conventional manner. The catheters were connected to Validyne transducers (± 200 cm H_2O; Validyne Corp., Northridge, CA). Electrical

(*Received in original form March 13, 2000 and in revised form February 9, 2001*)

Supported by the Royal Brompton Hospital Trustees.

Correspondence and requests for reprints should be addressed to Dr. M. I. Polkey, Respiratory Muscle Laboratory, Royal Brompton Hospital, Fulham Rd, London SW3 6NP, UK. E-mail: m.polkey@rbh.nthames.nhs.uk

This article has an online data supplement, which is accessible from this issue's table of contents online at www.atsjournals.org

Am J Respir Crit Care Med Vol 163. pp 1400–1403, 2001
Internet address: www.atsjournals.org

signals were amplified (Validyne) and passed via an analogue-to-digital converter (NB-MIO-16; National Instruments, Austin, TX) to an Apple Macintosh computer running LabView software (National Instruments) and sampling at 100 Hz.

Subjects exercised on a treadmill with monitoring of pulse oximetry and ECG. Minute ventilation and expired gas composition were measured breath by breath using an orifice pneumotachograph and mass spectrometer (Benchmark system; PK Morgan, Rainham, Kent, UK).

Protocol

Prior to exercise subjects were taught to produce short, sharp sniffs without measurable abdominal muscle activity (as judged by Pga) while seated in front of a monitor. After determining maximum sniff esophageal pressure (Sn Pes_{max}) (13) a series of submaximal sniffs of varying amplitude were recorded. These provided a baseline for subsequent comparison after exhaustive exercise; sniffs of varying amplitude were collected in order that sniffs obtained at exercise termination could be matched with baseline sniffs of similar amplitude. The patients with CHF then performed an incremental treadmill walk (Balke protocol) until severe breathlessness caused exercise termination. Sniffs were then recorded each minute for 5 min and also during the tenth minute after stopping. Esophageal and gastric pressures were also recorded during the treadmill walk. For the control group an identical protocol was followed except that exercise was discontinued when minute ventilation reached 100 L/min, this being greater than the highest value attained by any patient with CHF during the initial pilot studies.

Analysis

Maximum relaxation rate. In order to prevent expiratory muscle activity affecting the results, sniff traces were accepted for analysis only if the standard criteria (10) used in our laboratory were met. These were (*1*) Sniff maneuver performed at end-expiration, as determined by esophageal pressure. (*2*) Sniff duration less than 500 ms, with smooth, symmetrical upstroke and decay. (*3*) Decay of esophageal pressure curve returns to but does not exceed end-expiratory level. (*4*) Absence of abdominal muscle contraction during relaxation phase, determined by asymmetry of the gastric pressure trace. In the present study 1,507 of 2,415 sniffs (62%) met the criteria for analysis; this acceptance rate is comparable to our previous clinical studies (10, 14).

Sn Pes MRR was calculated using customized semiautomated LabView software, as the maximal rate of decay of pressure divided by peak pressure over a 50-ms epoch, with units of percent pressure loss/10 ms. Normalizing MRR pressure traces allowed comparison of traces with different amplitudes. As MRR varies between subjects, the effect of exercise on MRR was expressed as a percentage of baseline. As MRR recovers exponentially and returns to baseline within 5 min (8), we selected as the primary endpoint the percent slowing of MRR recorded in the first minute after cessation of exercise.

Respiratory muscle load. A measure of the pressure generated by the inspiratory muscles during the treadmill walk was obtained from the esophageal pressure time product (PTPes) and had units of cm $H_2O \cdot$ s/min. This was calculated by the software that integrated the esophageal trace during inspiration using a semiautomated program. In this analysis we defined inspiration by the start and finish of inspiratory airflow and for the esophageal pressure took the baseline to be zero; for a fuller discussion of this convention see Reference (15).

Statistics

Statistics were analyzed using an unpaired *t* test (Statview 4.0, Abacus Concepts, Berkeley, CA). A p value of < 0.05 was accepted as significant.

RESULTS

All the patients with CHF tolerated the protocol and all terminated walking because of intolerable dyspnea. In the online repository, Table E2 shows the exercise data obtained for the patients with CHF compared with the control subjects. Mean (SD) time to exhaustion for the patients with CHF was 9′19″ (3′32″) minutes and the time to achieve 100 L/min (or to severe dyspnea) was 11′32″ (3′55″) minutes for the control subjects (p = NS). The highest ventilation achieved by any patients with CHF was 99.9 L/min with a mean (SD) of 77.4 (8) L/min; the control subjects continued exercising until reaching a mean minute ventilation of 102.6 L/min ($p < 0.009$), except in the case of Subjects 8 and 9 who stopped at 31.7 L/min and 58.9 L/min, respectively. The work rate at exercise termination (calculated from treadmill speed and gradient) was not significantly different between the two groups, but maximum oxygen uptake was significantly greater at cessation in the control subjects whether expressed in absolute terms (mean difference, 13.4 mL/min/kg; 95% CI, 5 to 21 ml/min/kg; p = 0.0003) or as % predicted (mean difference, 34%; 95% CI, 19 to 50%; p = 0.0002). There were no significant differences between the two groups at the point of cessation of exercise for heart rate, respiratory rate, tidal volume, or inspiratory duty cycle. The work performed by the inspiratory muscles, estimated from the esophageal pressure time product (PTPes), during the first and last 30 s of the treadmill walk was 234 cm $H_2O \cdot$ s/min and 561 cm $H_2O \cdot$ s/min for the patients with CHF and 182 cm $H_2O \cdot$ s/min and 578 cm $H_2O \cdot$ s/min for the control subjects. There was no significant difference in PTPes between groups.

Representative traces from the exercise protocol and typical sniff traces obtained in a patient with CHF before and immediately after the walk to severe dyspnea are shown in Figure 1. The mean inspiratory MRR for the first minute after termination of exercise was 22.4% slower than baseline in the CHF group and 2.8% slower than baseline in the control group (p = 0.009). The mean difference in slowing of MRR between patients with CHF and control subjects was 19.9% (95% CI, 5.7 to 34%). The effect of exercise on slowing of mean MRR showed some overlap between groups (*see* Table 1). The frequency of slowing was six of the eight patients with CHF and four of the nine control subjects; this difference was not statistically significant. Nevertheless, even when only those who did slow were considered, the magnitude was greater in patients with CHF (mean difference, 14.5% greater in CHF; 95% CI, 5.7 to 23.3%). The mean (SD) MRR data for the two groups for the 10 min after the exercise protocol is shown in Figure 2 and demonstrates the rapid recovery of sniff Pes MRR in line with previous observations (10, 14).

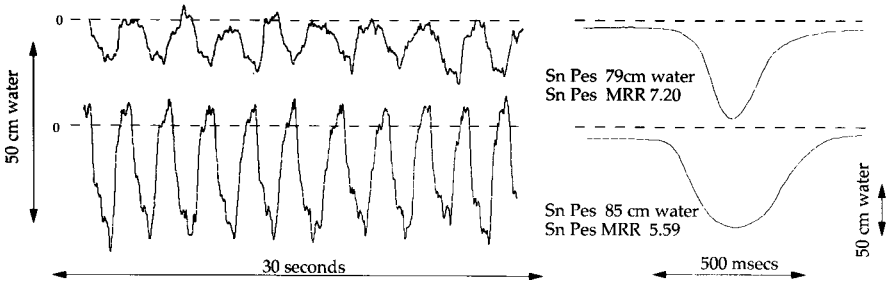

Figure 1. (*Left panel*) Representative esophageal pressure traces for the first (*upper record*) and last (*lower record*) 30 s of exercise in a patient with CHF. (*Right panel*) Representative sniffs before (*upper record*) and immediately after (*lower record*) exercise in the same patient.

TABLE 1. SNIFF PES DATA FOR PATIENTS WITH HEART FAILURE AND CONTROL SUBJECTS*

	Baseline Sn Pes MRR		Sn Pes MRR 1-Min Post Walk		
	Mean	SD	Mean	SD	% Change†
CHF					
1	8.09	0.88	6.17	0.53	23.7
2	7.51	0.47	4.92	0.47	34.5
3	7.56	0.57	5.80	0.67	23.3
4	8.30	0.34	5.74	0.50	30.8
5	6.93	0.59	6.67	0.60	3.8
6	7.48	0.43	7.46	0.51	0.3
7	7.49	0.93	4.48	0.66	40.2
8	7.22	0.74	5.44	1.00	24.6
Mean	7.62	0.60	5.89	0.56	22.4
SD	0.45	0.22	1.01	0.08	15.1
Control					
1	7.91	0.21	8.03	0.62	−1.5
2	8.06	0.75	8.05	0.62	0.1
3	6.34	0.63	6.72	0.28	−6.0
4	8.22	0.74	8.63	0.67	−5.0
5	8.05	0.73	6.48	0.64	19.5
6	8.20	0.73	10.04	0.46	−22.4
7	7.03	0.37	6.00	0.20	14.7
8	6.13	0.90	5.20	0.46	15.1
9	6.55	0.89	5.85	1.16	10.6
Mean	7.39	0.66	7.22	0.57	2.79
SD	0.87	0.23	1.56	0.28	13.39

Definition of abbreviations: CHF = chronic heart failure; MRR = maximum relaxation rate; Sn Pes = sniff esophageal pressure.

* Baseline values for Sn Pes MRR prior to and for the first minute after cessation of exercise. (Sn Pes MRR = maximum relaxation rate of esophageal pressure after a submaximal sniff.)

† A negative polarity indicates a MRR after exercise of a greater magnitude than baseline.

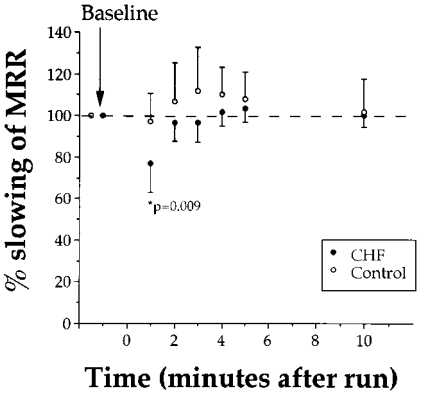

Figure 2. Mean (± SD) Sn Pes MRR as a percentage of baseline after exercise protocol. (Sn Pes MRR = maximum relaxation rate of esophageal pressure after a submaximal sniff.)

DISCUSSION

Our data show that slowing of inspiratory muscle MRR occurs in patients with CHF following treadmill exercise to the point of severe breathlessness, this occurred with a greater magnitude than was observed in control subjects. Before considering the possible causes and implications of these findings, methodologic aspects need to be considered.

Critique of the Methods

Subjects. Patient selection was based on the presence of dyspnea, rather than limb fatigue, as the limiting symptom during exercise. In terms of CHF severity they were not as severely impaired as participants in some studies (16, 17) but are likely to be reasonably representative of a stable outpatient clinic population.

Protocol. Our patients walked until severe dyspnea prevented further exercise, whereas normal subjects exercised to achieve a minute ventilation comparable to that in patients with CHF in order to determine whether the level of ventilation attained at peak exercise in CHF was associated with excessive inspiratory muscle loading in normal subjects. It is known that slowing of inspiratory muscle relaxation rate (8) can be demonstrated in well-motivated normal subjects after maximal isocapnic ventilation at rest and that diaphragm fatigue can be elicited if very high levels of ventilation are achieved during whole body exercise (18). Thus the purpose of the control group was to allow comparison of the effect of similar levels of ventilation with those achieved by the patients with CHF at peak exercise, rather than to investigate in normal subjects whether maximal exercise could produce slowing of inspiratory muscle MRR. For this purpose we consider the control group to be appropriate in that they achieved a higher proportion of predicted $\dot{V}O_2$max with no significant differences in the pattern of breathing in terms of respiratory rate, duty cycle, or pressure-time product at the point of discontinuing exercise. We therefore believe the finding that slowing of Sn Pes MRR is more pronounced in patients with CHF than in control subjects to be due to their disease.

Sniff maneuver. Measurement of MRR is an established method for determining the effect of loading on the inspiratory muscles in normal subjects (8, 9) as well as clinical situations such as COPD and after weaning from mechanical ventilation (19). Although fatigue affects muscle MRR, other potentially confounding factors that need to be considered include muscle length, sniff amplitude, and the effect of contraction of other respiratory muscles (20, 21). Nevertheless (as discussed in the online data supplement) these factors cannot undermine the conclusions drawn from this study.

Significance of the Findings

Cause of slowing of MRR in CHF. Slowing of MRR is an adaptive mechanism that occurs early in a fatiguing protocol and is attributed to several factors, including depletion of ATP, intracellular acidosis, and changes in transmembrane ion conductance. Our findings are consistent with the study by Davies and colleagues (22) (reported in abstract form), which found that exercise induced slowing of inspiratory muscle relaxation rate (judged from mouth pressure during a gasp) in patients with CHF. The identification of slowing in Sn Pes MRR is consistent with the hypothesis of an imbalance between the load placed on the respiratory muscle pump and its capacity.

Although there is only a modest reduction in respiratory muscle strength in CHF (5), *in vivo* work has shown deoxygenation of accessory respiratory muscles in patients with CHF during exercise, suggesting reduced perfusion (23). Although slowing of MRR is independent of hypoxia (10, 24), our data support the contention that changes in the intracellular milieu of the inspiratory muscles occurs in exercising patients with CHF. The hypothesis would then be that the inability of the heart to match the requirements of the exercising respiratory musculature resulted in the manifestation of excessive loading (slowing of Sn Pes MRR). The possibility that load is also increased in CHF because of bronchial hyperresponsiveness has been previously raised (25). Our data do not exclude the possibility that load is increased in CHF, although the fact that comparable levels of inspiratory muscle pressure generation resulted in comparable levels of minute ventilation between patients and control subjects argues against this being the predominant problem.

Slowing of MRR was not seen in two of eight patients with CHF; although both subjects were well motivated this may have been due to premature cessation of exercise (especially in Patient 5) or reflect the multifactorial nature of exercise limita-

tion in this condition. Both subjects had documented coronary artery disease; however, neither reported angina. Equally, four of nine control subjects had slowing of MRR, the greatest of which was 19.5% baseline. Nevertheless, even if the data from all participants with slowing of MRR are considered in isolation, the magnitude of slowing was greater in patients with CHF. Excessive loading causes slowing of MRR in healthy people (8), and therefore we interpret the current observations as supporting the concept that patients with CHF and control subjects represent two distinct (but overlapping) populations with respect to the effect of exercise on MRR. Patients with CHF seem to demonstrate slowing of the MRR earlier and to a greater extent than do control subjects. This is consistent with our starting hypothesis that excessive inspiratory muscle loading contributes to dyspnea. However, we acknowledge that patients with CHF seem to be "less abnormal" than patients with advanced COPD whose data we have previously reported (10). In such patients a greater mean slowing of MRR occurred at substantially lower levels of minute ventilation, and slowing was an invariable finding. In one subject MRR became faster after exercise; we speculate that this may represent abnormalities of chest wall or abdominal wall mechanics in this subject who was more obese than the remainder (BMI, 29 kg/m^2).

We have shown that slowing of inspiratory muscle MRR occurs in subjects with CHF during intensive exercise. This indicates that the inspiratory muscles are operating under excessive load in CHF, but it raises the issue of whether their endurance to fatigue is reduced. Slowing of MRR does not of itself fulfill the criteria for the presence of muscle fatigue (26), to determine this would require additional studies measuring the effect of exercise on more direct measures of contractility such as twitch transdiaphragmatic pressure. We believe such studies are now warranted. Diaphragm biopsies in subjects with severe CHF show increased proportions of fatigue-resistant type I muscle fibers (27) and there are changes in diaphragm contractility studied *in vivo* which may reflect this (5). Therefore, slowing of inspiratory muscle MRR at a lower level of whole-body exercise and with a similar degree of respiratory muscle loading, despite these adaptations, suggests a reduced endurance capacity, possibly secondary to impaired perfusion (23). Our study is, we believe, the first to demonstrate excessive inspiratory muscle loading in a physiologically realistic model.

In patients with severe COPD unloading of the inspiratory muscle pump using noninvasive ventilation (NIV) during exercise increases exercise endurance, and as consequence is developing a role in pulmonary rehabilitation (28). The present data suggest that NIV may also have a role to play in the rehabilitation of patients with CHF.

In summary our data provide evidence of excessive loading of the inspiratory muscle pump during exhaustive exercise in patients with severe CHF. Further studies are indicated to elucidate the underlying mechanisms and clinical significance of these findings.

References

1. Buller NP, Jones D, Poole-Wilson PA. Direct measurement of skeletal muscle fatigue in patients with chronic heart failure. *Br Heart J* 1991; 65:20–24.
2. Harrington D, Anker SD, Chua TP, Webb-Peploe KM, Ponikowski PP, Poole-Wilson PA, Coats AJ. Skeletal muscle function and its relation to exercise tolerance in chronic heart failure. *J Am Coll Cardiol* 1997; 30:1758–1764.
3. Christie R, Meakins J. The intrapleural pressure in congestive heart failure and its clinical significance. *J Clin Invest* 1934;13:323–345.
4. Evans SA, Watson L, Cowley AJ, Johnston IDA, Kinnear WJM. Static lung compliance in chronic heart failure: relation with dyspnoea and exercise capacity. *Thorax* 1995;50:245–248.
5. Hughes PD, Polkey MI, Harrus ML, Coats AJ, Moxham J, Green M. Diaphragm strength in chronic heart failure. *Am J Respir Crit Care Med* 1999;160:529–534.
6. Mancini D, Donchez L, Levine S. Acute unloading of the work of breathing extends exercise duration in patients with heart failure. *J Am Coll Cardiol* 1997;29:590–596.
7. O'Donnell DE, D'Arsigny C, Raj S, Abdollah H, Webb KA. Ventilatory assistance improves exercise endurance in stable congestive heart failure. *Am J Respir Crit Care Med* 1999;160:1804–1811.
8. Mulvey DA, Koulouris NG, Elliott MW, Laroche CM, Moxham J, Green M. Inspiratory muscle relaxation rate after voluntary maximal isocapnic ventilation in humans. *J Appl Physiol* 1991;70:2173–2180.
9. Esau SA, Bellemare F, Grassino A, Permutt S, Roussos C, Pardy RL. Changes in relaxation rate with diaphragmatic fatigue in humans. *J Appl Physiol* 1983;54:1353–1360.
10. Kyroussis D, Polkey MI, Keilty SEJ, Mills GH, Hamnegard C-H, Moxham J, Green M. Exhaustive exercise slows inspiratory muscle relaxation rate in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1996;153:787–793.
11. Polkey MI, Harris ML, Hughes PD, Hamnegard C-H, Lyons D, Green M, Moxham J. The contractile properties of the elderly human diaphragm. *Am J Respir Crit Care Med* 1997;155:1560–1564.
12. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir J Suppl* 1993;16:5–40.
13. Laroche CM, Mier AK, Moxham J, Green M. The value of sniff esophageal pressures in the assessment of global inspiratory muscle strength. *Am Rev Respir Dis* 1988;138:598–603.
14. Polkey MI, Kyroussis D, Mills GH, Hamnegard C-H, Keilty SEJ, Green M, Moxham J. Inspiratory pressure support reduces slowing of inspiratory muscle relaxation rate during exhaustive treadmill walking in severe COPD. *Am J Respir Crit Care Med* 1996;154:1146–1150.
15. Polkey MI, Kyroussis D, Hamnegard CH, Mills GH, Hughes PD, Green M, Moxham J. Diaphragm performance during maximal voluntary ventilation in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1997;155:642–648.
16. Mancini DM, Henson D, LaManca J, Levine S. Respiratory muscle function and dyspnea in patients with chronic congestive heart failure. *Circulation* 1992;86:909–918.
17. Mancini DM, Henson D, LaManca J, Levine S. Evidence of reduced respiratory muscle endurance in patients with heart failure. *J Am Coll Cardiol* 1994;24:972–981.
18. Johnson BD, Babcock MA, Suman OE, Dempsey JA. Exercise-induced diaphragmatic fatigue in healthy humans. *J Physiol (Lond)* 1993;460: 385–405.
19. Goldstone JC, Green M, Moxham J. Maximum relaxation rate of the diaphragm during weaning from mechanical ventilation. *Thorax* 1994; 49:54–60.
20. Mulvey DA, Koulouris NG, Elliott MW, Moxham J, Green M. Maximal relaxation rate of inspiratory muscle can be effort-dependent and reflect the activation of fast-twitch fibers. *Am Rev Respir Dis* 1991;144: 803–806.
21. Levy RD, Esau SA, Bye PT, Pardy RL. Relaxation rate of mouth pressure with sniffs at rest and with inspiratory muscle fatigue. *Am Rev Respir Dis* 1984;130:38–41.
22. Davies SW, Jordan SL, Pride NB, Lipkin DP. Respiratory muscle failure on exercise in chronic heart failure. *Circulation* 1990;82:III-24.
23. Mancini DM, Ferraro N, Nazzaro D, Chance B, Wilson JR. Respiratory muscle deoxygenation during exercise in patients with heart failure demonstrated with near-infrared spectroscopy. *J Am Coll Cardiol* 1991;18:492–498.
24. Bark H, Supinski G, Bundy R, Kelsen S. Effect of hypoxia on diaphragm blood flow, oxygen uptake, and contractility. *Am Rev Respir Dis* 1988; 138:1535–1541.
25. Cabanes L, Costes F, Weber S, Regnard J, Benvenuti C, Castaigne A, Guerin F, Lockhart A. Improvement in exercise performance by inhalation of methoxamine in patients with impaired left ventricular function. *N Engl J Med* 1992;326:1661–1665.
26. NHLBI Workshop Summary. Respiratory muscle fatigue. Report of the Respiratory Muscle Fatigue Workshop Group. *Am Rev Respir Dis* 1990;142:474–480.
27. Tikunov B, Levine S, Mancini D. Chronic congestive heart failure elicits adaptations of endurance exercise in diaphragmatic muscle. *Circulation* 1997;95:910–916.
28. Polkey MI, Hawkins P, Kyroussis D, Ellum SG, Sherwood R, Moxham J. Inspiratory pressure support prolongs exercise induced lactataemia in severe COPD. *Thorax* 2000;55:547–549.