

490. Exercise testing in disease

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**Inspiratory resistive loading exacerbates calf vasoconstriction in patients with coexisting COPD-CHF compared to COPD and healthy controls**

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**Rationale:** Sympathetic overstimulation is a marker of chronic heart failure (CHF) and might also be present in advanced chronic obstructive pulmonary disease (COPD). Inspiratory resistive loading (IRL) can trigger a sympathetically-mediated metaboreflex which increases peripheral vascular resistance, leading to impaired blood flow. Coexistence of COPD and CHF is likely to potentiate these abnormalities.

**Objective:** To investigate the effects of IRL on calf blood flow (CBF) and resistance (CVR) in patients with COPD presenting or not with CHF as a co-morbidity and healthy controls.

**Methods:** Twelve patients with COPD on isolation (FEV<sub>1</sub> = 42±14% pred), 10 patients with coexisting COPD-CHF (FEV<sub>1</sub> = 46±10% pred, left ventricular ejection fraction < 45%) and 10 age-matched controls breathed through an inspiratory resistance at 60% of maximal inspiratory pressure (MIP) to task failure. CBF was measured by venous occlusion plethysmography.

**Results:** COPD-CHF had significantly lower MIP than COPD and controls (p<0.05). The former group, however, stopped earlier the IRL trials (185±35 s vs. 284±82 s vs. 365±88 s, respectively; p<0.01). COPD-CHF had lower CBF and higher CVR in this former group. In addition, IRL led to greater decrements in CBF and increases CVR in COPD-CHF compared to either COPD or controls (p<0.05). CVR during IRL was inversely related to MIP across the groups (r = -0.66, p<0.01).

**Conclusions:** CHF as a co-morbidity of COPD exacerbates peripheral vasoconstriction induced by inspiratory muscle overloading. This might contribute to further impair muscle blood flow during exercise in this patient sub-population.

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**Effects of exercise on ubiquitination and proteasome activity in skeletal muscle in COPD patients**

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**Objective:** COPD patients have reduced exercise capacity and skeletal muscle function. The aim of this study was to investigate exercise effects on proteasome activity in skeletal muscle of COPD patients. We wanted to evaluate ventilatory limited and unlimited exercise by comparing whole body training against small isolated muscle training. The effects of oxidative stress and systemic inflammation were also evaluated.

**Methods:** In total, 21 patients with moderate to severe COPD were studied. Spirometry, peak oxygen uptake (VO<sub>2-peak</sub>), ubiquitin activity, proteasome activity, protein carbonylation and systemic inflammation were measured before and after a 10 week aerobic exercise program (n=14) and a 6 week knee extensor exercise program (n=7). Five age- and sex-matched healthy individuals served as reference group.

**Results:** At baseline all COPD groups had reduced proteasome activity compared to controls (p<0.05). When comparing the effects of the two modes of exercise, only whole body aerobic exercise resulted in increased proteasome activity in both the aerobic interval and the moderate continuous group. We found no differences in carbonylation or protein ubiquitination. Serum levels of TNFα and IL-6 were not influenced by training.

**Conclusion:** COPD patients have altered skeletal muscle proteasome activity and whole body aerobic exercise training induces an increased proteasome activity compared to isolated muscle training. The increase exclusively in the whole body exercise groups could therefore suggest an inappropriate skeletal muscle response, and could imply that training small muscle groups is better for COPD patients.

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**Muscle remodelling is blunted in hypoxic COPD patients after pulmonary rehabilitation**

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Pulmonary rehabilitation in COPD patients aims at increasing exercise tolerance, partly through improving muscle function. The influence of chronic hypoxia on the training-induced muscle adaptations has not been specifically investigated.

We studied muscle adaptations and exercise capacity following 2 months of endurance and resistance exercises in 8 COPD patients with long term oxygen therapy (hypoxic group) and 15 without arterial oxygen desaturation (normoxic group). Biopsies of the vastus lateralis were analyzed before and after training for fiber size, citrate synthase activity, and markers of protein synthesis/degradation. At baseline both groups did not differ in pulmonary function, fat free mass, or exercise capacity. Maximal workload and walking distance improved in both groups but to a greater extent in the hypoxic group (27.5 versus 10.5%, p= 0.06; 23.7% versus 6.9%, p= 0.01, respectively). Fiber cross sectional area and citrate synthase activity increased significantly in the normoxic group only (both p<0.05). Levels of phosphorylated AKT, p70S6K and GSK3β tended to increase with training in the normoxic group in favour of an upregulation of anabolism while decreased significantly in the hypoxic group (p=0.01). mRNA levels of anabolic genes (IGF1, MGF) and catabolic genes (MurF-1, Atrogin, Foxo-1 and -3, Myostatin) did not change with training in both groups.

We conclude that in COPD patients with chronic hypoxemia, pulmonary rehabilitation improved exercise capacity while the markers of muscle remodelling remained unchanged. It deserves to be studied whether changes in genes expression occurred earlier during rehabilitation in these patients.

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**Distinguishing pulmonary hypertension in interstitial lung disease by ventilation and perfusion defects as measured by cardiopulmonary exercise testing**

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**Introduction:** Pulmonary hypertension (PH) is common in interstitial lung disease (ILD) and is associated with worse prognosis. Comparing ventilation (VD) and perfusion defects (PD) on cardiopulmonary exercise testing (CPET) can detect PH, but has not been assessed in ILD.

**Aims and objectives:** We proposed using CPET to detect PH in patients with ILD by assessment of VD and PD by mixed expired CO<sub>2</sub> (PeCO<sub>2</sub>) and end-tidal CO<sub>2</sub> (PetCO<sub>2</sub>).

**Methods:** 75 patients with ILD referred for CPET were included who had pulmonary function tests, right heart catheterization, CPET all done within 4 months of each other. Data were assessed at rest, end of unloaded warm up (WU), ventilatory threshold (VT), and peak exercise (PE) for PeCO<sub>2</sub>, PetCO<sub>2</sub>, PeCO<sub>2</sub>/PetCO<sub>2</sub> and the activity pattern of PeCO<sub>2</sub> versus PetCO<sub>2</sub>.

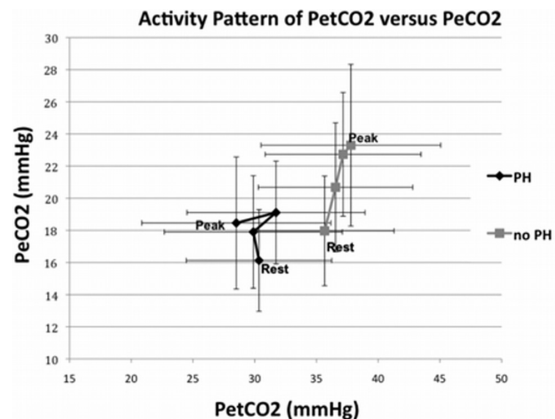
**Results:** ILD patients with PH demonstrated significantly lower PetCO<sub>2</sub> and PeCO<sub>2</sub> at all levels of exercise and low PeCO<sub>2</sub>/PetCO<sub>2</sub> only at WU.

VD and PD in CPET in ILD patients

		PetCO <sub>2</sub> (mmHg)	PeCO <sub>2</sub> (mmHg)	PetCO <sub>2</sub> /PeCO <sub>2</sub>
Rest	PH	30.3	16.1	0.54
	No PH	35.7*	18.0*	0.51
WU	PH	29.9	17.9	0.61
	No PH	36.5*	20.7*	0.57*
VT	PH	32.7	19.1	0.61
	No PH	37.2*	22.7*	0.61
PE	PH	28.5	18.5	0.66
	No PH	37.9*	23.3*	0.62

\*p<0.05.

Activity pattern has marked changes with exercise in ILD patients with PH.



**Conclusions:** Evaluation of ventilation and perfusion defects by CPET can detect pulmonary hypertension in patients with ILD.

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**Effects of sildenafil intake on the dynamics of skeletal muscle oxygenation at the onset of and recovery from exercise in CHF**

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**Rationale:** Nitric oxide (NO) exerts an important role in temporally and spatially match microvascular O<sub>2</sub> delivery (Q'O<sub>2mv</sub>) to utilization in the skeletal muscle.

**Objective:** To investigate the effects of increased nitric oxide (NO) bioavailability induced by sildenafil intake on muscle Q'O<sub>2mv</sub>-to-oxygen uptake (V'O<sub>2</sub>) matching at the transition to and from exercise in patients with chronic heart failure (CHF).

**Methods:** 10 males (ejection fraction= 27±6%) underwent a supra-gas exchange threshold exercise test to the limit of tolerance 1 hour after sildenafil (50 mg) or placebo intake. The dynamics of V'O<sub>2</sub>, fractional O<sub>2</sub> extraction in the vastus lateralis (~ [deoxy-Hb+Mb]) by near infrared spectroscopy, and cardiac output (CO) were evaluated by non-linear regression procedures.

**Results:** Sildenafil increased exercise endurance compared to placebo by ~ 20%, an effect that was related to faster on- and off-exercise V'O<sub>2</sub> kinetics (p<0.05). Active treatment, however, failed to accelerate CO dynamics (p>0.05). On-exercise [deoxy-Hb+Mb] kinetics were slowed by sildenafil with a subsequent response "overshoot" being significantly lessened or even abolished. In contrast, [deoxy-Hb+Mb] recovery was faster with sildenafil (~ 15%). Improvements in muscle oxygenation with sildenafil were closely related to faster on-exercise V'O<sub>2</sub> kinetics and greater increases in exercise capacity (p<0.05).

**Conclusions:** Sildenafil intake enhanced on- and off-exercise Q'O<sub>2mv</sub>-to- V'O<sub>2</sub> matching and V'O<sub>2</sub> kinetics with positive consequences on exercise tolerance in CHF. The lack of effect on CO suggests that improvement in blood flow to and within skeletal muscles underlies these effects.

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**Effects of proportional assist ventilation on skeletal muscle reoxygenation after high-intensity exercise in chronic heart failure**

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**Background:** Respiratory muscle unloading can enhance the haemodynamic responses to exercise thereby allowing a closer matching between skeletal muscle O<sub>2</sub> delivery and utilization in patients with chronic heart failure (CHF).

**Objective:** To assess whether proportional assist ventilation (PAV), compared to sham ventilation, would improve the dynamic coupling between microvascular O<sub>2</sub> delivery and O<sub>2</sub> uptake (V'O<sub>2</sub>) during recovery from heavy-intensity exercise in patients with CHF.

**Methods:** Twelve patients with CHF (NYHA class II and III and left ventricle ejection fraction= 26±9%) underwent two high-intensity, constant-work rate (80% peak) cycle ergometer tests receiving PAV or sham ventilation. Off-exercise kinetics of the "primary" component of V'O<sub>2</sub>, an index of fractional O<sub>2</sub> extraction by near infrared spectroscopy (~Δ[deoxy-Hb+Mb]) in the vastus lateralis and cardiac output (QT) by impedance cardiography were assessed.

**Results:** PAV speeded the recovery kinetics of all variables compared to sham ventilation.

Table 1: Kinetic parameters for sham and PAV ventilation

	Sham	PAV	p value
τV'O <sub>2p</sub> (s)	76.7±13.5	55.9±7.0	0.03
τΔ[deoxy-Hb+Mb] (s)	42.3±6.9	31.2±5.9	0.008
MRT QT (s)	88.5±15.4	46.7±4.0	0.02

Values are means ±SE. V'O<sub>2p</sub> = Pulmonary oxygen uptake, τ = constant time, MRT = mean response time, QT = cardiac output, Δ[deoxy-Hb+Mb] = variation of deoxyhemoglobin + myoglobin concentration by NIRS.

**Conclusions:** These data indicate that PAV has beneficial effects on recovery of muscle metabolism and central haemodynamics after high-intensity exercise in CHF patients.

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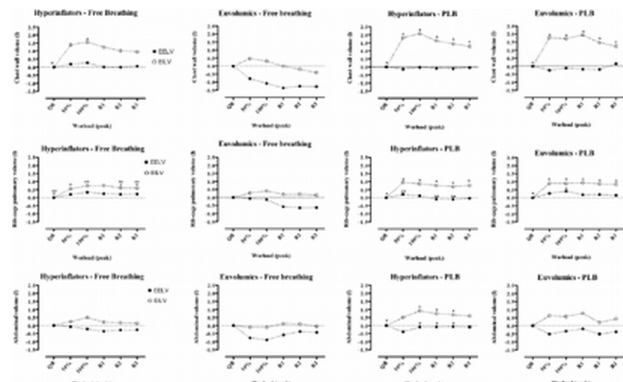
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**Dynamic hyperinflation and effects of pursed lips breathing on chest wall kinematics during exercise in patients with asthma**

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To assess the effects of exercise on lung volumes and the influence of Pursed Lips Breathing (PBL) on operational lung volumes in asthma patients. In 14 patients, 33.9±10 years/old, FEV1%:65.7±18.6, lung volumes were assessed by

opto-electronic plethysmography. Two incremental submaximal cycling test (ISET) sets based on 3 min. rest, 1 min. unloaded pedaling and 30w increase in workload every min. during free breathing and PLB were done. We identified two patterns of changes in operational volumes at 100%max. workload in free breathing. Patients that increase End Expiratory Lung Volume (EELV) ΔEELV=0.27±0.5L and developed Dynamic Hyperinflation (DH), hyperinflators (HG, n=6) and patients that decrease EELV euolumics (EG, n=6) ΔEELV=-1.07±0.8 L. Rib cage pulmonary (RCp) was the main responsible to increase in EELV in HG. Variation of End Inspiratory Lung Volume (ΔEILV) in HG was significantly different from EG, 1.5±0.8 vs 0.31±0.4. PLB induced changes in EILV in both groups during in chest wall and RCp compartment. In abdominal compartment ΔEILV significantly increased with PLB in all moments except at 50%max. workload. PLB induced changes on EELV in RCp compartment at 100%max. workload in EG and at 50%max. workload, 1st and 2nd recovery time in HG.



Exercise induces different changes in operation lung volume in patients with asthma. PLB modulate breathing pattern and improve operational lung volumes.

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**Reliability of the 6-minute walk test in patients referred for pulmonary rehabilitation**

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**Introduction:** The 6-minute walk test (6mwt) has been widely used as an easy assessment of physical performance and as an outcome parameter in pulmonary rehabilitation (PR). However, uncertainty remains about the need to perform multiple tests because of the possible occurrence of a learning effect contributing to the reliability of the test.

**Aims and objectives:** The aim of this study was to evaluate the reliability of three consecutive 6mwt in a large group of patients referred for PR.

**Methods:** From June 2006 to December 2011, 1112 patients referred to a PR center performed a 6mwt on 3 consecutive days (t1-3) as part of the routine pre-PR assessment. Tests were performed during a clinically stable period according to the guidelines of the American Thoracic Society. Retrospectively, absolute differences between the tests were evaluated and correlation coefficients between the three tests were calculated.

**Results:** The mean distance of the 6mwt (mean m SD) was 352m/122 m on t1, 378±124 on t2 and 393±125 m on t3. All differences between the tests were statistically significant (p<0.001). 51% of patients walked their maximal distance on t3 but only 8% on t1. When considering a minimal clinical important difference (MCID) of 54 m, 35% of the patients showed differences beyond the MCID in favour of t3 when compared to t1, 11% when compared to t2 and 22% when t2 was compared with t1. Significant correlations exist between t1-t2 (r=0.933, p<0.001), t1-t3 (r=0.912, p<0.001), t2-t3 (r=0.951, p<0.001).

**Conclusion:** These data show that a single 6mwt is not reliable in these patients with severe pulmonary disease. At least two 6mwt are required to obtain a reliable test.