66. Altered mechanisms during exercise in disease

376

Late-breaking abstract: Impaired carbon monoxide diffusion capacity is the strongest predictor of exercise intolerance, even in moderate COPD

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Background: Exercise intolerance is the hallmark of COPD and FEV_1 is the traditional method used to define the severity of COPD. However there is a dissociation between FEV_1 and exercise capacity in a large proportion of subjects with COPD. Therefore it is of interest to investigate if other lung function parameters are having an additive, predictive value of exercise capacity (EC) and if this differs according to the COPD stages.
Methods: Spirometry, measurements of lung volumes and diffusing capacity for carbon monoxide (DLCO) were performed in 88 patients with COPD GOLD stages II-IV. EC was determined by symptom-limited incremental cycle ergometer test.
Results: DLCO, FEV_1 and inspiratory capacity (IC) were found to be the best predictors of EC in a stepwise regression analysis and explain 72% of EC. These lung function parameters explained 71% of EC in GOLD II, 69% in GOLD III and 32% in GOLD IV. DLCO alone was the best predictor of exercise capacity in GOLD II and IV (Table).

Predictive values of FEV_1, IC and DLCO for exercise capacity in diffrent GOLD classes

	GOLD II	GOLD III	GOLD IV
FEV_1	0.27*	0.53*	0.13*
IC	0.42*	0.41*	0.17*
DLCO	0.69*	0.51*	0.29*

Numbers are presented as R^2 values from a simple regression model. *Indicates significant relation.

Discussion: Additive information regarding COPD patients' exercise capacity is obtained by measuring diffusing capacity and inspiratory capacity. DLCO was the strongest predictor of exercise capacity in all subjects and the best individual predictor in patients with GOLD stage II. This suggests that clinically monitoring with measurements of diffusing capacity may be beneficial even in patients with moderate disease severity.

377

ACE gene polymorphisms, COPD exercise tolerance and response to acute oxygen

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Introduction: Recent studies have shown that polymorphisms of the angiotensin-converting enzyme (ACE) gene are closely associated with pulmonary disorders.The aim of this study was 1) to investigate the impact of ACE gene polymorphism on exercise tolerance 2) to determine whether a relationship exists between oxygen responses and differential genotype (DD, DI or II).
Methodology: Twenty-four COPD patients [FEV1=51±2.4%pred] exhibiting exercise-induced desaturation performed endurance exercise at 60% of their maximal workload in two randomised conditions: normoxia and hyperoxia. ACE genotype was determined for each patient. Endurance time (Tlim), dyspnoea, cardiac output (CO) and arterio-venous difference in oxygen (AVD) were compared.
Results: In normoxia, Tlim was greater for DI than DD (1168 vs 541s; $p<0.05$). Oxygen supply improved performance in both groups, but DI again exhibited better endurance than DD (1313 vs 1132s; p=0.01). This better exercise capacity in DI was associated with a greater AVD and decreased CO for comparable oxygen uptake. Although O2 significantly increased Tlim in two-thirds of patients (R+) and significantly decreased it in about one-third (R-), R+ and R- proportion was comparable in the two genotype groups (chi^2=0.52, p=0.46).
Conclusion: This study showed that I-allele was associated with better endurance performance. Although DD and DI increased performance with oxygen, responses were associated with differential consequences on cardiovascular and peripheral muscle adaptations. However, ACE polymorphism could not be related to positive or negative oxygen responses.

378

Influence of abdominal volume regulation on chest wall hyperinflation during constant work rate exercise in patients with COPD

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It has been recently reported that some patients with chronic obstructive pulmonary disease (COPD) may actively recruit the expiratory abdominal (AB) muscles in order to avoid exercise-related dynamic hyperinflation. It remains unclear, however, whether this strategy is universally efficacious in counterbalancing the potential increases in rib cage (RC) volumes thereby promoting a net deflating effect on chest wall (CW). Thirty males with COPD (FEV_1= 43.8±9.5%) performed a constant work rate cardiopulmonary exercise test (75% max) to the limit of tolerance (Tlim) on a cycle ergometer. Breath-by-breath ventilatory kinematics was continuously monitored by optoelectronic plethysmography (BTS, Italy). End-expiratory volume of the RC (EEV_{RC}) and EEV_{CW} significantly increased from rest to Tlim in 17 patients. EEV_{AB} remained stable in 9 of them ("non-recruiters/hyperinflators"); in contrast, it decreased slightly in 7 "recruiters/hyperinflators" thereby lessening CW hyperinflation. EEV_{RC} remained stable and EEV_{AB} decreased sharply in the remaining 13 "recruiters/non-hyperinflators". "Recruiters/hyperinflators" showed higher dyspnoea scores and the worst exercise capacity (~80% lower than the "recruiters/non-hyperinflators") ($p<0.05$). In conclusion, CW deflation secondary to extensive AB recruitment was restricted to COPD patients showing no evidences of RC hyperinflation. On the other hand, pronounced increases in RC volumes were associated with milder degrees of AB recruitment. Although this avoided more severe CW hyperinflation, it was related to intense breathlessness and poor exercise tolerance. Supported by: FAPESP and CNPq, Brazil

379

Effect of heliox breathing on locomotor and respiratory muscle oxygen delivery during exercise in COPD patients with or without dynamic hyperinflation

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Background: Dynamic hyperinflation and large intrathoracic pressure swings induce negative hemodynamic effects during exercise in COPD. Heliox breathing reduces the degree of dynamic hyperinflation thereby improving peripheral muscle oxygen delivery. Whether this effect also applies to patients who do not hyperinflate during exercise, is unknown.
Methods: 17 COPD patients (n=8 hyperinflators [FEV_1=37±4% pred] and n=9 non-hyperinflators [FEV_1=48±4% pred]) performed two constant-load exercise tests to the limit of tolerance in air and whilst breathing heliox.
Results: The improvement in exercise tolerance by heliox was not different between hyperinflators and non-hyperinflators (by 3.8±1.9 and 4.2±2.0 min, respectively).This is probably due to the finding that systemic oxygen delivery significantly improved in both hyperinflators (from 1.48±0.10 to 1.70±0.13 l/min) and non-hyperinflators (from 1.68±0.12 to 1.93±0.15 l/min); however, the mechanism of improvement was different as heliox improved cardiac output in non-hyperinflators (from 9.3±0.5 to 10.4±0.5 l/min) whilst arterial oxygen content increased only in hyperinflators (from 160±3 to 177±4 mlO_2/l). Nonetheless, quadriceps and intercostal muscle oxygen delivery (measured by NIRO+ICG method with arterial sampling) improved significantly and by the same magnitude in both hyperinflators (by 16.6±7.4 and 4.0±1.1 mlO_2/min/100g, respectively) and non-hyperinflators (by 17.6±8.2 and 4.5±1.2 mlO_2/min/100g, respectively).
Conclusion: Heliox improves peripheral and respiratory muscle oxygen delivery in all COPD patients regardless of the occurrence of exercise-induced dynamic hyperinflation.

380

Effects of oxygen supplementation on cerebral oxygenation during progressive exercise in patients with COPD and healthy controls

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The rate of change (Δ) in cerebral oxygenation (COx) during exercise is modulated by cerebral blood flow and arterial O_2 content (CaO_2). It is currently unclear whether ΔCOx would (i) be impaired during exercise in patients with chronic obstructive pulmonary disease (COPD) who are not overtly hypoxaemic and (ii) improve with hyperoxia (HiOX, FIO_2= 0.4) in these patients. Twenty non-hypercapnic males with COPD (FEV_1= 47.2±11.5% predicted) and 9 age- and gender-matched controls underwent incremental exercise tests under HiOX and normoxia (NOX). ΔCOx was determined by near infrared spectroscopy (fold-changes in HbO_2) and cardiac output (QT) by impedance cardiography. A significant drop in SpO_2 was found in 8/20 patients (peak SpO_2= 86±2% vs. 96±2% for "desaturators" (DESAT) and "non-desaturators" (NONDESAT), respectively. In NOX, ΔCOx was lower in DESAT *versus* NONDESAT and controls; in contrast, mean arterial pressure (MAP) was higher in the former group ($p<0.05$). Increases in SpO_2 with HiOX were particularly pronounced in DESAT (86±2 vs. 99±1%); interestingly, a significant improvement in COx was found only in this group (0.52±0.20 vs. 2.09±0.42; $p<0.01$). There was no significant effect of HiOX on QT in control and COPD groups; MAP, however, decreased in DESAT ($p<0.05$). ΔCOx is impaired in patients with COPD who desaturate during progressive exercise even if they are not entitled to long-term O_2 therapy. O_2 supplementation (FIO_2= 0.4) is able to correct for these abnormalities, an effect that was related to enhanced CaO_2 rather than improved cerebral haemodynamics. Supported by: CNPq and FAPESP, Brazil.

381

Locomotor muscle afferents contribute to ventilatory control during exercise in heart failure patients

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Background: Reduced ventilatory efficiency is a hallmark of heart failure (HF) and is linked to disease severity and worse prognosis. Mechanisms responsible for altered ventilatory efficiency remain poorly understood but may include neurologic feedback from locomotor muscles. This study was designed to determine the impact of blocking locomotor muscle afferent feedback on ventilation (V_E) during exercise in HF patients.
Methods: 5 HF patients with reduced systolic function (age=60±11 yrs, ht=1.81±0.03 m, wt=94±7 kg, ejection fraction 27±5%, NYHA class 2±0) underwent two 5 minute submaximal steady-state exercise sessions at 60% peak work (placebo-PLA vs regional neural blockade via intrathecal injection of fentanyl-RNB). Breath-by-breath measures included V_E, breathing frequency (fb), tidal volume (V_T), end-tidal carbon dioxide ($P_{ET}CO_2$), oxygen consumption (VO_2), and carbon dioxide production (VCO_2). Central chemoreceptor sensitivity was also measured via CO_2 rebreathe.
Results: At end exercise, there was no difference in VO_2 (1.4±0.2 vs 1.4±0.2 L/min, p=0.43). whereas V_E was reduced with RNB (48.0±6.5 vs 41.8±6.0 L/min, $p<0.05$) through a reduction in fb (27.2±5.2 vs 23.9±4.2 breaths/min, $p<0.01$) with no change in V_T (1.8±0.2 vs 1.8±0.2 L/min, p=0.81). Additionally, the V_E/VCO_2 ratio was reduced (improved) with RNB (33.2±3.5 vs 28.2±2.8, $p<0.05$). After exercise, there was no difference between the conditions for chemoreceptor sensitivity ($V_E/P_{ET}CO_2$ slope=2.4±0.9 vs 2.4±0.6, p=0.80).
Conclusion: In HF patients, blocking afferent neural feedback from the locomotor muscles during exercise reduces V_E and improves ventilatory efficiency. Funded by NIH/NCRR grant KL2-RR024151.

382

Comparing cardiopulmonary responses to incremental exercise in patients with chronic thromboembolic pulmonary hypertension and idiopathic pulmonary arterial hypertension

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Patients with chronic thromboembolic pulmonary hypertension (CTPH) are more likely to develop proximal obstructive lesions than those with idiopathic pulmonary arterial hypertension (IPAH). Therefore, CTPH might present with poorer right ventricle-pulmonary vascular coupling, worse ventilation-perfusion matching, and lower maximal exercise capacity compared to IPAH. We comparatively evaluated 26 patients with CTPH and 14 with IPAH who underwent a symptom-limited incremental exercise test on a cycle ergometer. Haemodynamic variables (systolic volume [SV] and cardiac index [CI]) were measured by impedance cardiography. Baseline characteristics were similar in CTPH and IPAH (age 48±16 *vs* 40±17 yrs; CI 2,0±0,5 *vs* 2,2±0,6 L/min/m^2; pulmonary vascular resistance 14±5 *vs* 16±8 Wood; $p>0,05$). Metabolic, cardiovascular and haemodynamic parameters also did not differ between the groups (peak $V'O_2$ 11±3 *vs* 12±3 mL/kg/min; $\Delta V'O_2/\Delta W$ 7,3±1,7 *vs* 7,1±1,7; peak SV 84±13 *vs* 86±22 mL; peak CI 6,5±1,0 *vs* 6,9±1,6 L/min/m^2; $p>0,05$). However, CTPH patients had higher $\Delta V'E/\Delta V'CO_2$ (75±26 *vs* 52±17; $p<0,05$), lower end-tidal CO_2 pressure at the anaerobic threshold (21±5 vs 28±6 mmHg; $p<0,05$) and greater oxyhaemoglobin desaturation (peak SpO_2 88±7 vs 93±5, $p<0,05$). In conclusion, patients with CTPH had higher sub-maximal ventilatory response to progressive exercise compared to those with IPAH. Although this difference did not impact upon peak exercise capacity, it indicates that CTPH led to more extensive pulmonary gas exchange abnormalities despite similar resting and exercise haemodynamic impairment.

383

Do respiratory mechanics abnormalities contribute to exertional dyspnoea in patients with pulmonary hypertension?

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We examined the impact of changes in ventilatory profile and dynamic operating lung volumes during symptom-limited incremental cardiopulmonary cycle exercise testing (CPET) on the intensity of dyspnoea in patients with pulmonary hypertension (PH). Twenty non-smokers PH patients (n=13 idiopathic, n=7 chronic thromboembolic disease) with no evidence of spirometric obstruction (FEV1/FVC = 85±7% pred) and 10 age-matched healthy subjects performed a CPET to the limit of tolerance. Ventilatory profile, operating lung volumes [derived from inspiratory capacity (IC) measurements], and dyspnoea intensity (by Borg scale) were assessed throughout CPET. In 70% of PH patients (n=14), IC decreased progressively throughout CPET by 0.35L on average (dynamic hyperinflation), whereas in all healthy subjects IC increased by 0.2L. Dyspnoea intensity and minute ventilation (V'E) were greater in PH patients at any stage of CPET compared with healthy controls: at standardized work rate of 60watts, dyspnoea rating and V'E were 5 Borg units and 45L/min respectively in PH patients compared with 1 Borg unit and 33L/min respectively in healthy subjects. At standardized V'E of 60L/min, PH patients presented with greater dyspnoea (by 4 Borg units) and dynamic hyperinflation (by 0.3L) compared with healthy controls. Dynamic hyperinflation and the excessive ventilatory response to CPET seem to be potential contributors to increased exertional dyspnoea intensity in patients with PH.
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