Late-breaking abstract: Comparative analysis of cardiopulmonary and clinical responses to six minute walking test and maximal exercising test in obese women

Luciana Di Thommazo-Luporini, Soraia Pilon Jürgensen, Viviane Castello, Camila Negrão Dias, Rafael Luís Luporini, José Carlos Bonjorno-Júnior, Claudio Ricardo de Oliveira, Aparecida Maria Catai, Audrey Ilorghi-Silva. Physiotherapy, Federal University of Sao Carlos, Sao Carlos, SP, Brazil Medicine Department, Federal University of Sao Carlos, Sao Carlos, SP, Brazil Interunits Post Graduate Program in Bioengineering, University of Sao Paulo, Sao Carlos, SP, Brazil

Background: The six minute walking test on the treadmill (tread6MWT) can be an efficient method to evaluate the functional capacity in obese population comparable to cardiopulmonary exercising test (CPET).

Aims: To compare the cardiopulmonary and subjective responses to tread6MWT and CPET in obese and eutrophic women.

Methods: Fourteen obese women were recruited to obese group (OG) and 15 women to eutrophic group (EG). Both groups performed a CPET and a tread6MWT. Cardiopulmonary variables and dyspnea level were registered. Absolute limits of agreement between cardiopulmonary and subjective responses to CPET and tread6MWT were assessed by Bland-Altman analysis.

Results: OG presented higher oxygen uptake (V'O₂), minute ventilation (V'E), and systolic blood pressure (SBP) than EG (p<0.05) in both tests. There is a
strong correlation (r=0.76) between V' O2 and body mass index in the CPET, as well as heart rate (HR) in the peak of both tests (r=0.77) in OG. The dyspnea was higher during CPET than treadmill (p=0.05) in both groups. It was observed the agreement of both tests to identify relative V' O2, V'E, SBP and HR at the peak of exercise, presenting a mean difference between the tests of: 6.0±5.6 (mL/kg/min), 29.0±16.9 (L/min), 17.5±19.4 (mmHg) and 32.9±19.4 (bpm), respectively (HIAS-LSD).

Conclusions: The treadmill was able to promote metabolic and cardiopulmonary responses in agreement to the CPET. The treadmill seems to be an appropriate method to evaluate the functional limit and value in obese women without submitting them to such a significant dyspnea as the CPET does.

Financial support: FAPESP (09/01842-0) and CAPES.

Paper Discussion
Room G102-103 - 08:30-10:30

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**P4729**

Late-breaking abstract: Time-dependent effect of acute hypoxia on brain excitability in healthy humans

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Some studies have shown altered cortex excitability in hypoxemic patients suffering from COPD or OSAS. Recently, contradictory results regarding the effect of hypoxia (H) on cortex excitability have been reported in healthy subjects, possibly depending on the experimental protocols. We evaluated the effects of 1 and 3 hours H on motor cortex excitability, intrinsic cortical inhibition and supraspinal voluntary activation (VA) using transcranial magnetic stimulation (TMS). TMS to the quadriceps cortex area and femoral nerve electrical stimulations were performed in normoxia and H (FiO2 = 12%) in 10 healthy subjects. Motor-evoked potentials (MEPs) at 50-100% maximal voluntary contraction - MVC), recruitment curves (MEPs at 30-100% maximal stimulator power output at 50% MVC), cortical silent periods (CSP) and VA were measured. One hour H did not modify any parameters of brain excitability but reduced VA probably due to the repetition of contractions 1-h apart (98.2±% vs. 95±%: p=0.01). Conversely, 3 h significantly increased i) MEPS of the rectus femoris (RF), vastus lateralis (VL) and vastus medialis (VM) at all force levels (e.g. at 50% MVC, RF: +26±%, VL: +15±%, VM: +17±%); and ii) VA at all force levels, and at 50% MVC RF: +23±%, VL: +27±%, VM: +24±% (all p<0.05), but did not modify VA (98.1±% vs. 97.2±%: p=0.21). These data demonstrate a time-dependent H-induced increase in cortex excitability and intra-cortical inhibition, without changes in VA. Thus, the transition from physical or cognitive performance needs to be elucidated to better understand the effects of hypoxemia in patients.

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**P4730**

Late-breaking abstract: Association between serum surfactant protein D (SP-D) and lung function measurements in self-reported healthy twins

Sofia Lockmann1, Quisha Tan2, Anders Schlosser1, Ingrid Tilsted3, Uffe Holmlov1, Kirsten Kyvik1, Gitte Sørensen1, 1Department of Cardiovascular and Renal Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark; 2Department of Pulmonary Medicine, Odense University Hospital, Odense, Denmark; 3Institute of Regional Health Services Research, University of Southern Denmark, Odense, Denmark

Introduction: Serum SP-D is suggested to serve as a biomarker in various pulmonary diseases, and has been showed negatively correlated to FEV1 in COPD. Serum SP-D is suggested to serve as a biomarker in various pulmonary diseases, and has been showed negatively correlated to FEV1 in COPD. The purpose of the present study was to investigate the association between serum SP-D and lung function normal Danes.

Material and methods: Data of serum SP-D originates from 1,476 self-reported healthy twins. Association between variables were analyzed by using a multiple linear regression model using SP-D as response variable and pre-bronchodilator FEV1 and FVC as explanatory variables. Intra-pair dependency was taken into account, and data was adjusted for sex, age and BMI.

Results: There was a significant difference in mean serum SP-D levels in smokers with and without obstruction. (p<0.05) See table 1. Association for SP-D of FEF25-75 and FEV1 was found to be negative in smokers (p=0.0013) and non-smokers (p=0.0330).

<table>
<thead>
<tr>
<th>SP-D</th>
<th>FEV1% pred</th>
</tr>
</thead>
<tbody>
<tr>
<td>NO (N=91)</td>
<td>NO (N=38)</td>
</tr>
<tr>
<td>96±4</td>
<td>96±4</td>
</tr>
<tr>
<td>90±43</td>
<td>106±529</td>
</tr>
<tr>
<td>134±753</td>
<td>134±753</td>
</tr>
<tr>
<td>1850±1068</td>
<td>1850±1068</td>
</tr>
</tbody>
</table>

Conclusion and perspectives: Findings indicate opposite phenotypic correlation between SP-D and FEV1 in smoking and non-smoking individuals. Further analysis of available data will include multivariate twin modelling to investigate whether there is a genetic correlation between the traits and genetic association analysis to find out whether such a genetic correlation could be explained by single nucleotide polymorphisms within candidate genes such as the SPFTP gene.

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**P4731**

Late-breaking abstract: Determination of anaerobic threshold through different methodologies during ramp protocol in elderly healthy men

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For assessing the cardiopulmonary integration during aerobic exercise, anaerobic threshold (AT) has been an important index of performance. Additionally, the respiratory compensation threshold (RCT) has been used for determining performance of quasi-maximum intensities (Wasserman et al., 1983). The aim of this study to identify the anaerobic threshold (AT) obtained from the V-slope method, visual inspection of oxhemoglobin (O2Hb) and desoxihemoglobin (HHb) curves and compare findings with the heteroscedastic (HS) method applied to VCO2, heart rate (HR) and HbHb data. Fourteen healthy men were subjected to cardiopulmonary testing (CPX) on a cycle-ergometer until physical exhaustion. Biological signals collected during CPX included: ventilatory variables; spectroscopy by NIRS; and HR by a cardiofrequency meter. We observed temporal equivalence and similar values of power, VO2 (mL/min), VO2 (mL kg^-1 min^-1) and HR at AT by the detection methods used. In addition, by the Blomquist-Alman plot (Fig. 1), HR confirmed the good agreement between the methods with biases between -1.3 and 3.5 bpm.

In conclusion: (i) all detection methods were sensitive in identifying AT, including the HS applied to HR and HR by a method showed good correlation in the identification of AT. Thus the results support the HR seems to be a valid parameter in determining the AT of the individuals in our study (Grants: FAPESP)

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**P4732**

Cytokine expression in the diaphragm of rats breathing against subacute hypoxic conditions

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COPD patients show muscle damage and an increase in the expression of local cytokines in their diaphragm. The paracrine role of these cytokines is still unclear.

Objective: To analyze the effects of subacute hypoxia on the diaphragm muscle. Methods: Wistar rats (n=9/group) were exposed to: (1) hypoxia (FIO2 0.10) +placebo, (2) normoxia +placebo, (3) hypoxia +Ifliximab [monoclonal antibody that results in the blockade of TNF-a receptors], and (4) normoxia +Ifliximab for 2 weeks in all cases. At the end of the study period diaphragm and gastrocnemius muscles as well as blood samples were obtained. Molecular and cellular indices of muscle damage, oxidative stress, cytokine expression and activation of regeneration pathways were obtained using morphometry, Western-blots, spectrophotometry, ELISA, luminometry and RT-PCR.

Results: Although rats exposed to hypoxia showed higher levels of expression of different cytokines (TNF-a, IL-6, INF-g) in their diaphragms than the control animals, no differences were observed in muscle damage, oxidative stress and biomarkers of muscle regeneration. Inhibition of TNF-a action in hypoxic animals resulted in an even higher expression of local cytokines with no relevant changes in the ether variables when compared with hypoxia animals receiving placebo. No changes were observed in either limb muscle or blood in any of the groups.

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Conclusions: Hypoxia induces local inflammation in respiratory muscles of hy- poxic rats. This effect appears to be selective for respiratory muscles and can be related to changes in their mechanical loading and its mismatching with the oxygen delivery to the muscle.

Funded: SAFO7-62719, CIBERES, SEPAR & SCOP.

P4733 The impact of aerobic exercise on lung inflammation and remodeling in experimental emphysema

Isabela Guimarães1, Giselle Padilha1, Miquéias Lopes-Pacheco1, Patricia Marques1, Mariana Antunes1, Nazareth Rocha2, Edison Assis3, Hugo Farra-Neto4, Raquel Magalhães1, Debora Xisto1, Patricia Rocco1, 1Laboratory of Pulmonary Investigation, Carlos Chagas Filho Biophysics Institute, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil; 2Department of Physiology, Fluminense Federal University, Niterói, Brazil; 3Laboratory of Immunopharmacology, FIOCRUZ, Rio de Janeiro, Brazil.

This study investigated the impact of aerobic exercise on lung inflammation and remodeling in experimental emphysema. 32 BALB/c mice were assigned into 2 groups. In control (C) animals, saline was intratracheally (i.t.) injected, whereas emphysema mice received porcine pancreatic elastase (ELA, 0.1 UI, i.t). Saline and ELA were i.t. injected once a wk during 4 wks. After the last wk, C and emphysema groups were further randomized into subgroups: sedentary and exercise. Exercise mice ran on a motorized treadmill, at moderate intensity (8-12 m.min⁻¹), 5% grade, 30 min/day, 3 times a wk for 4 wks. 24 h after the last session, lung mechanics and morphometry, as well as cytokines and total cell count in bronchoalveolar lavage fluid (BALF) and blood were measured. Echocardiographic analysis was done before and after emphysema induction and at the end of the experiment. The sedentary emphysema group presented, compared to C: 1) reduced lung static elastance; 2) increased lung hyperinflation and elastic fiber content; 3) augmented levels of KC (murine interleukin (IL)-8 homolog), tumor necrosis factor-α, interferon-γ, and IL-10; and 4) pulmonary arterial hypertension, evidenced by increased pulmonary flow acceleration. Aerobic exercise: 1) improved lung mechanics; 2) reduced lung hyperinflation, and the number of cells and levels of these cytokines in BALF and blood; 3) diminished elastic fiber content, and 4) restored pulmonary flow acceleration to C values. In conclusion, aerobic exercise modulated the inflammatory process and acted on lung remodeling, improving pulmonary function. Supported by: INCIT/INOFAR, FAPERJ, PRONEX, CNPq

P4734 Regular and moderate exercise prevents airway remodeling in a murine model of chronic allergic asthma

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The present study investigated whether regular and moderate aerobic exercise might prevent airway remodeling in experimental chronic allergic asthma. For this purpose, BALB/c mice were assigned into 2 groups: sedentary (S) and trained (T). Tr group ran on a motorized treadmill, at moderate intensity (8-12 m.min⁻¹), 5% grade, 30 min/day, 3 times a wk for 8 wks. At 8 wks, animals were further ran- domized into 2 subgroups to be immunized and challenged with ovalbumin (OVA) or to receive saline using the same protocol (C). Aerobic exercise continued until the end of the protocol. Echocardiographic analysis was done before, at 4 and 8 weeks of training, and after asthma induction. Twenty-four hours after the last challenge, trained, compared to sedentary mice, presented: 1) an increase in systolic output, left ventricular mass, and end-diastolic volume; 2) a reduction in airway resistance, viscoelastic pressure, static elastance, eosinophil infiltration, smooth-muscle actin expression, and collagen fiber content in airways and lung parenchyma; 3) a decrease of transforming growth factor-β levels in bronchoalveolar lavage fluid (BALF) and blood; 4) an increase in interferon-γ in BALF and blood; 5) an augment of interleukin (IL)-10 in blood but a reduction in BALF; and 6) a decrease in IL-5 and IL-13 only in BALF. In conclusion, regular and moderate aerobic exercise was effective in preventing airway and lung parenchyma remodeling in the present murine model of chronic allergic asthma, improving lung function. Supported by: INCIT/INOFAR, CNPq, PRONEX, FAPERJ, CAPES

P4735 Repeated mannitol or NaCl hyperosmolar exposure of bronchial epithelial cells to mimic exercise-induced airways damage

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Hyperosmolality of the airway surface lining fluid might be involved in exercise-induced airway epithelial damage. Hyperosmolality causes release of interleukin 8 (IL-8) by bronchial epithelial cells (BEC) in vitro, but the effects of repeated hyperosmolar exposure on BEC are unknown. 16HBE cells were exposed to NaCl or Mannitol (Mann) (320, 640, 960, 1280 mOsM/kg H2O) in culture medium for 1 or 40 min for 3 consecutive days; at 24 h after each exposure, supernatants were collected and stored at -80 °C for subsequent IL-8 measurements (R&D System, UK). Cell viability was examined by MTT assay. MTT was assessed by Western Blot. Repeated exposure to NaCl or Mann for 10 min at any concentration did not affect IL-8 release. Exposure of 16-HBE cells to NaCl or Mann at 640-1280 mOsM/kg H2O for 40 min increased IL-8 concentration at days 1 and 2 compared to untreated cells (p < 0.001); however, IL-8 release decreased at days 2-3 compared to day 1 (p < 0.05). Repeated NaCl or Mann treatment for 10 min decreased cell viability by 10-20% (p < 0.001), while hyperosmolar exposure for 40 min decreased cell viability in a dose-dependent manner at day 1 and dramatically at days 2-3 (>60% for NaCl, >40% for Mann at highest concentrations, p < 0.001). NaCl was cytotoxic compared to Mann (p < 0.05). PINK expression increased dose-dependently with hyperosmolality at days 1-2; IL-8 decreased at day 3; IL-8 release was blocked by a specific JNK inhibitor (SP600125). Therefore, hyperosmolar exposure acutely activates BEC through JNK activation, whereas repeated hyperosmolar exposures repeated for 3 days decrease IL-8 release likely due to major epithelial damage.

P4736 Acute exposure to mechanical forces deteriorates lung structure and function in a mouse model of emphysema

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Mechanical forces have been suggested to accelerate the deterioration of lung structure and function in emphysema. To test this, we used C57BL/6 mice treated with porcine pancreatic elastase (N=48) or left intact as controls (N=16). At 2, 7 or 21 days after treatment, mice were ventilated (Vt=6 μl/g, 240/min) for 1 h with inspiratory pressure without deep inspiration. To dilute lung pathology, we used 35-40 μl/kg airway pressure at 30 Hertz for 21 days. FRC was measured in a plethysmograph and tissue elastance (H) was calculated from respiratory impedance. After the experiment, lungs were fixed at 20 hPa pressure and sections were stained with hematoxylin-eosin or a modified Verhoeff method to visualize elastin. Independent of time, DI increased FRC and independent of DI, FRC increased with time (p < 0.001). Compared to control, H decreased in the no-DI 7- and 21-day groups (p < 0.001, p < 0.001). Compared to H, DI decreased in the DI groups (p < 0.001). DI and FRC improved with time (p < 0.001). In conclusion, no-DI, DI and FRC improved over time and these parameters were significantly different from the control group. DI and FRC are useful as biomarkers to assess pulmonary function in emphysema.

P4737 Aerobic exercise training attenuates the decrease in heart rate variability induced by exposure to cigarette smoke in mice

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Smoking has been shown to influence the tone of the autonomic nervous system as reflected by heart rate variability (HRV) a predictor of increased cardiac risk and aerobic exercise (AE) training has been described as capable to modulate the HRV. Objective: This study evaluated the temporal effects of aerobic exercise in the HRV in mice exposed to cigarette smoke (CS).

Methods: C57Bl6 mice were divided in 4 groups: Control, Smoke, Smoke and Exercise/Smoke (Smoke/Exercise). Smoke groups were exposed to CS for 30min/day (twice), 5days/week for 12 weeks. Exercise groups were trained at moderate intensity for 40min/day, 5days/week for 12 weeks. HRV was measured at baseline and 2, 4, 6, 8, 10 and 12 weeks after the last CS exposure and/or AE session. HRV was measured by ECG, ratios of (very low frequency [VLF] + high frequency [HF])/total power. The following parameters were used: heart rate (HR), HRV for time domain (standard deviation of normal beats [SDNN] and root mean square of successive differences in the heart beat interval [RMSSD]) and frequency domain (low frequency [LF], high frequency [HF] and LF/HF ratio).

Results: Exposure to CS decreased SDNN and RMSSD values after 6 weeks (p < 0.001, compared to control group) where it remained until 10 weeks and AE training reverted this effect. Exposure to CS also decreased HF only after 6 weeks (p < 0.01) compared to control group and this effect was reverted to AE training.

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Poster Discussion

Room G102-103 - 08:30-10:30
Conclusion: Our results suggest that AE training at moderate intensity have beneficiales effects on cardiac autonomic nervous function, a clinically relevant predictor of cardiovascular morbidity and mortality, in mice exposed to cigarette smoke.

P4738 Site of ROS production by mitochondria of skeletal muscle of patients with COPD
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Introduction: The role of iron deficiency (IDe) on exercise intolerance has not been explored in patients with COPD. We hypothesized that IDe could represent a potentially treatable factor in the functional impairment of COPD patients.

Methods: We evaluated 80 COPD patients (FEV1 1.3±1.5 pred; PaO2 71±11 mmHg; BMI 27±4 kg/m²; Charlson Index 2.5±1.2; 18% current smokers) without anemia. IDe was defined as a ferritin level <100 μg/L, or a ferritin level between 100-299 μg/L, and a transferrin saturation <20%. We measured both cycloergometer endurance time (ET) and six minute walking distance (6MWd) to evaluate associations between treatment and IDe.

Results: Forty percent (n=32) of the patients showed IDe. Iron deficiency did not show association with demographic or pulmonary function variables. But, patients with IDe showed lower ET (3.26±2.5 vs. 3.62±2.21, sec, p<0.01) and decreased 6MWd (OR de 3.82; IC: 1.22-8.81, p=0.018). Moreover, endurance training response assessed by ET was lower in IDe patients (A265±64 vs. A45±82 sec > than the in COPD without such deficiency.

Conclusions: IDe shows a high prevalence in COPD patients and discloses a significant association with aerobic capacity. Evaluation of the potential benefit of a specific treatment of IDe in COPD appears to be warranted.

P4741 Predictors for developing hypoxic respiratory failure in COPD – A 3-year follow-up
Erum Waatevik Saure1, Tomas M.L. Eagan2, Robert L. Jensen3, Per S. Bakke1, Marianne Voll-Aanerud2, Einar Thorsen1, Jon A. Hardie1, 1Institute of Medicine, University of Bergen, Bergen, Norway; 2Department of Thoracic Medicine, Haukeland University Hospital, Bergen, Norway; 3Respiratory Medicine, Maastricht University, Maastricht, Netherlands.

Background: The risk of developing respiratory failure rises with increasing severity of COPD. Still, it is unknown which clinical and pulmonary function measurements are associated with subsequent development of hypoxic respiratory failure.

Methods: 401 subjects from the Bergen COPD Cohort Study, aged 40-75 years, GOLD stage II-IV, underwent repeated clinical and pulmonary function measurements including arterial blood gases over 3 years. Sex, age, smoking, and baseline measures of FEV1, RV/TLC-ratio, PaO2, PaCO2, and Fat Free Mass Index (FFMI) were analyzed as possible predictors for developing hypoxemia. We used both bivariate Cox proportional hazards analyses, with the time from baseline normoxemia until the first event of hypoxemia (PaO2 <80 mmHg) as a measure of event free time. 73 (18%) of the 401 patients were hypoxemic at baseline and excluded from the analyses.

Results: Within the three years of follow-up, a total of 46 patients (14%) developed hypoxemia. In bivariate Cox proportional hazards analyses, baseline FEV1, RV/TLC, FFMI, PaO2, and PaCO2 were significantly associated with developing hypoxemia. After multivariate Cox proportional hazards analyses, the following measures remained significantly associated with developing hypoxemia:

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV/TLC ratio (%)</td>
<td>1.014 (1.003–1.025)</td>
<td>0.012</td>
</tr>
<tr>
<td>PaO2 (kPa)</td>
<td>0.220 (0.129–0.375)</td>
<td>0.00</td>
</tr>
<tr>
<td>FFMI (kg/m²)</td>
<td>0.907 (0.830–0.992)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Conclusion: High RV/TLC ratio, low PaO2, and low fat free mass index were predictors for developing hypoxic respiratory failure in a 3 years follow-up of COPD patients.

P4742 Plasma vitamin D concentration and clinical characteristics in clinically stable patients with moderate COPD
Elisabeth Romme1, Ludwine Graat-Verboom1, Erica Rutten2, Frank Smeenk1, Martijn Spruit1, Emiel Wouters3, 1Respiratory Medicine, Catharina Hospital, Eindhoven, Netherlands; 2Program Development Centre, Centre of Expertise for Chronic Organ Failure, Horn, Netherlands; 3Respiratory Medicine, Maastricht University Medical Centre, Maastricht, Netherlands.

Introduction: Vitamin D deficiency is associated with poor functional performance in patients with COPD. However, most research is limited to patients with severe COPD, whilst vitamin D deficiency also occurs in GOLD stage II patients (Janssens et al. Thorax 2010). Therefore, we aimed to investigate differences in clinical characteristics in clinically stable GOLD stage II patients with and without vitamin D deficiency.

Methods: 159 patients with COPD GOLD stage II (age 69±7 yrs; FEV1 75%±9 pred; 58% men) recruited at the outpatient consultation office of the Catharina Hospital were included. Vitamin D deficiency was defined as plasma 25(OH)D concentration <50 nmol/L. BMI, FEV1, RV/TLC, arterial PO2, MRC dyspnea.

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six-minute walk distance (6MWD) and score on the BODE index were assessed. The number of sunshine hours 2 months before blood sampling was determined using data from the Royal Netherlands Meteorological Institute.

**Results:** Vitamin D deficient patients had higher RV/TLC, lower pO2, worse 6MWD, higher BODE score and less sunshine hours.

**Vit D deficient, N=77**

<table>
<thead>
<tr>
<th>Variable (units)</th>
<th>Sea level</th>
<th>Altitude Day 2 &amp; 3</th>
<th>Placebo</th>
<th>Sildenafil</th>
<th>Sildenafil + Sixtasentan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vc/Va (L/min)</td>
<td>100 (12.3) 110 (12.1)</td>
<td>110 (12.3)</td>
<td>110 (12.3)</td>
<td>110 (12.3)</td>
<td>110 (12.3)</td>
</tr>
<tr>
<td>DmCO/Va (%)</td>
<td>111 (23.9)</td>
<td>111 (23.9)</td>
<td>111 (23.9)</td>
<td>111 (23.9)</td>
<td>111 (23.9)</td>
</tr>
<tr>
<td>Sunlight hours</td>
<td>2#* 73</td>
<td>2#* 73</td>
<td>2#* 73</td>
<td>2#* 73</td>
<td>2#* 73</td>
</tr>
</tbody>
</table>

**Conclusion:** Patients with CMS have a preserved aerobic capacity with a ventilatory response identical to LL at sea level but blunt ventilatory adaptation compared to HH and LL at altitude likely explained by preserved oxygen delivery because of increased hemoglobin. This study was supported by a grant from Pfizer.