504. Innovative methods in clinical physiology

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Late-breaking abstract: Lung recruitment in normal and emphysematous rats during methacholine challenge

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Elastase-induced emphysema in rodents is characterized by enlarged alveoli and decreased lung elastance but generally no change in airway resistance. We studied airway and tissue mechanics and recruitment in rats before and during constrictor challenge.

Sprague-Dawley rats were treated by intratracheal instillation of 50 U porcine pancreatic elastase (PPE, n=6). Three weeks later, these animals and 6 controls (C) were anesthetized, tracheotomized and mechanically ventilated. From low-frequency impedance (Zrs), Newtonian resistance (RN), tissue damping (G), elastance (H) and hysteresivity (η=G/H) were estimated. The lungs were degassed in vivo with oxygen breathing (10 min) and tracheal occlusion (10 s), and then reinflated to 35 hPa, while the pressure-volume (PV) relationship and intratracheal crackle sound (Cra) were recorded. Measurements of Zrs, PV and Cra were repeated during i.v. infusion of methacholine (Mch) at 64 μg/kg/min.

RN was not different between groups PPE and C at baseline (44±4 vs 46±10 hPa.s/l) and during challenge (165±41 vs 176±37 hPa.s/l). G and H, respectively, were significantly lower in the PPE group compared to the controls (613±57 vs 839±165 hPa/l, and 2273±301 vs 3033±385 hPa/l), although their elevations due to Mch were similar (71±43% vs 79±34% for G, and 24±13% vs 25±20% for H). Whereas cumulative crackle intensity reached 80% at similar P levels in both groups, the recruited volume was more reduced during challenge (-39 vs -16%) in the PPE group.

In summary, while airway resistance and recruitment remained unaffected, the tissue damage was associated with an enhanced tissue constrictor response following elastase treatment.

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The measurement of absolute lung volume without plethysmography

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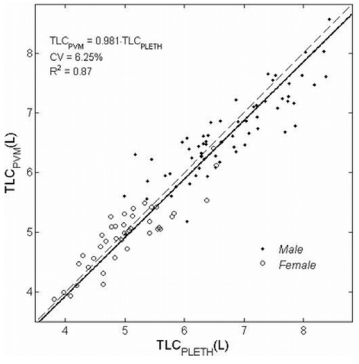
A basic and important component of pulmonary function testing is determination of absolute lung volumes, including total lung capacity (TLC). However this involves the use of equipment such as a Body Plethysmograph (BP) that is unsuited to routine office practice. To determine TLC, we report here a new mechanical approach – the Partial Volume Method, PVM – that requires neither BP, gas dilution, nor thoracic imaging, yet is simple, compact, rapid, inexpensive, and accurate.



With cheeks supported, the subject breathes through a flow interruption valve downstream of a parallel chamber of known gas volume. As a result of respiratory system inertance, respiratory flow continues undiminished for a very short time (<15 ms) after valve closure. This continuing flow compresses chamber gas in a manner inferable from Boyle's law, and used to deduce instantaneous absolute thoracic gas volume. In 106 healthy adults (40 women, 30.1±11.5 y, 22.8±4.1 BMI; 66 men, 29.1±10.2y, 24.0±3.1 BMI), TLC was measured using both PVM and standard plethysmography (ZAN 500, nSpire, Inc). For the combined group, $TLC_{PVM} = 0.981 \cdot TLC_{PLETH}$, R^2=0.87; R=0.943 (Pearson), CI: 0.961-0.918. The coefficient of variation (CV) for repeated PVM trials was 3.44%. Together, these results establish a new method for accurate, rapid, and reproducible determination of TLC in healthy subjects with minimal subject cooperation.

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Influence of end-expiratory level and tidal volume on ventilation distribution

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Background: Our understanding of regional filling of the lung and regional ventilation distribution (VD) is based on studies using radio labelled tracer gases. We aimed to investigate whether these results can be reprduced and differences in regional filling and spatial VD can be detected with electrical impedance tomography (EIT) in adults at different end-expiratory levels (EEL) and tidal volumes (V_T).

Methods: EIT measurements were performed in 10 healthy adults in right lateral position. Five different EEL with four different V_T at each EEL were tested in random order, resulting in 19 combinations. There were no measurements for the combination of the highest EEL/highest V_T as it was not possible to achieve this breathing pattern. EEL and V_T were controlled by visual feedback. The fraction of ventilation directed to the right lung (V_{right}) and the rate of regional filling (right lung vs. total lung) were analysed.

Results: Visual feedback resulted in distinct differences in EEL and V_T. V_{right} increased with increasing EEL and was <0.5 (more air directed to the left lung) only at the lowest EEL ($p<0.05$). With low EEL the filling of the right lung during the initial phase of the inspiration was slower ($p<0.05$) and the filling the lungs became more even with increasing EEL. With increasing V_T V_{right} increased significantly ($p<0.05$) and the filling characteristics changed towards more uneven ventilation.

Conclusion: The effect of different EEL and V_T on spatial and temporal VD during spontaneous tidal breathing in right lateral position can be assessed by EIT. Our results are in line with previous studies and suggest that the effect of EEL on ventilation distribution is greater than the effect of V_T.

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K-edge subtraction (KES) synchrotron imaging allows quantitative measurement of regional aerosol deposition, lung ventilation and airway morphology in rabbit

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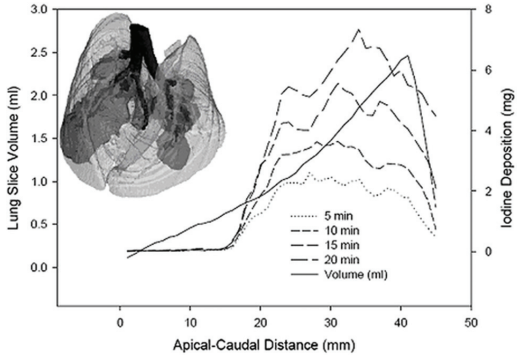
Rationale: The simultaneous measurement of regional lung ventilation, aerosol deposition and the anatomic configuration of airways are crucial for the better understanding of the determinants of aerosol deposition heterogeneity. However, no single imaging modality currently allows the acquisition of all such data simultaneously. The goal of this study was to test the feasibility of KES imaging to this end.

Methods: We used KES synchrotron radiation imaging [AJRCCM, 2009;180:296–303] to quantify regional lung ventilation, and the deposition of iodine (Iomeprol 88 mg/ml in NaCl 0.9%), delivered using an ultrasonic nebulizer (mass median aerodynamic diameter: 2.6±0.1 μm), in a healthy anesthetized, and mechanically ventilated rabbit (2.8 kg) in upright position. Regional ventilation images were obtained in 4 axial slices during inhalation of 70% Xe in O_2. Regional iodine deposition images were obtained in 45 contiguous slices after 0, 5, 10, 15 and 20 minutes of nebulization.

Results: See figure. Aerosol deposition showed significant spatial heterogeneity in normal lung. Inset: 3D rendering of central conducting airways (dark) and iodine (medium) and parenchyma (light grey).



Conclusions: These data demonstrate the feasibility of K-edge subtraction imaging for the quantitative measurement of regional aerosol deposition, lung ventilation and airway morphology *in vivo*.

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Chest wall kinematics in patients with osteogenesis imperfecta (OI)

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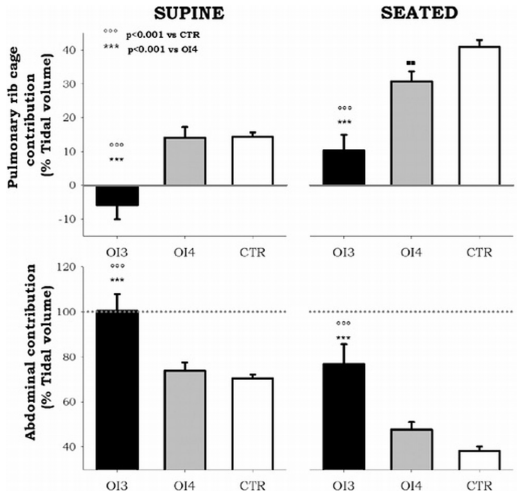
In Osteogenesis imperfecta (OI), an inherited connective tissue disorder characterized by brittle bones and significant chest wall (CW) deformities, pulmonary complications are the principal causes of death.In order to study how OI alters chest wall function, we studied 7 patients with severe form type III (OI3), 15 with moderate form type IV (OI4) and 26 healthy subjects (CTR). Breathing pattern, regional CW volume changes and thoracoabdominal asynchronies at rest in seated and supine position were measured by opto-electronic plethysmography. Rib cage deformities was assessed from OEP markers by computing the angle of the sternum (α) on the transversal plane.In both positions, minute ventilation was lower in OI than CTR because of lower tidal volume ($p<0.01$). Abdominal tidal volume in OI3 was higher and associated to low pulmonary rib cage contribution which was even negative (inspiratory paradoxical inward motion) in supine (figure).OI3 showed reduced α angle (161.6±17.5°; 178.3±10.5°; 181.7±12.9° in OI3, OI4 and CTR, $p<0.01$) and higher thoracoabdominal asynchony (labored breathing index=1.32±0.4, 1.03±0.03, 1.02±0.02 in OI3, OI4 and CTR, $p<0.001$).



In conclusion, OI3 is characterized by rib cage deformities (pectus carinatum) which alters CW function during breathing.The reduced or paradoxical rib cage motion during inspiration is compensated by an increased action of the diaphragm at rest, associated with large thoracoabdominal asynchrony.

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Diaphragm fatigue in self-paced running exercise of different durations

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Introduction: Diaphragm fatigue (DF) was shown to develop during high intensity constant-load exercise (CLE) above 85% of maximal oxygen consumption (VO_{2max}). CLE does, however, not appropriately reflect field trial conditions where exercise intensity is regulated by complex feedforward and feedback mechanisms, possibly aiming to reduce/prevent DF. Therefore, the development of DF was assessed in 11 well-trained athletes (age=31±4 yrs, VO_{2max}=66.7±4.6 $mlmin^{-1}kg^{-1}$) in 15 and 30min running time trials (TT). We hypothesized that DF would be larger in the 30TT where more time is spent above 85%VO_{2max}.

Methods: Before and 4min after completion of the TTs, esophageal and gastric pressures were assessed to calculate transdiaphragmatic twitch pressures ($P_{di,tw}$) during cervical magnetic stimulation.

Results: All subjects developed DF ($P_{di,tw}$ reduction, $\Delta P_{di,tw} \geq 10\%$) in the 15TT and 7/11 subjects in the 30TT. On average, $\Delta P_{di,tw}$ was 23.0±6.5 (15TT) and 18.5±12.1% (30TT; p=0.13). Mean exercise intensities were 89.4±3.5 (15TT) and 86.0±3.7%VO_{2max} (30TT; p=0.07) with similar mean durations above 85%VO_{2max} (11.9±2.0min; range: 7-14min; 15TT) and (16.2±9.7min; 1-28min; 30TT; p=0.19). The individual between-TT difference in $\Delta P_{di,tw}$ did not correlate with the difference in time spent above 85%VO_{2max} (R^2=0.20) but correlated with the difference in the average exercise intensity above 85%VO_{2max} (R^2=0.49; p=0.02).

Conclusion: In TT-conditions, the degree of DF is not related to the duration spent above 85%VO_{2max} but it is related to the exercise intensity when exercising above the 85%VO_{2max}-threshold.

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Ultrasound measurement of quadriceps wasting in patients with GOLD stage II COPD and its relationship to physical activity

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Introduction: Ultrasound measurement of rectus femoris cross-sectional area ($USRF_{CSA}$) is a radiation-free measure of muscle bulk that relates to quadriceps strength.[1] A recent study reported that a significant proportion of GOLD stage II patients have quadriceps weakness.[2] We hypothesised that quadriceps wasting, measured by $USRF_{CSA}$, would be observed in GOLD stage II patients and would correlate with daily physical activity levels.

Methods: $USRF_{CSA}$ and quadriceps maximum voluntary contraction (QMVC) were measured as described by Seymour *et al* [1]. Physical activity was recorded for six consecutive days using a multisensor biaxial accelerometer, SenseWear Pro Armband™. Fat free mass (FFM) was estimated using bioelectrical impedance and a disease specific regression equation.

Results: We studied 100 patients with stable COPD, (GOLD stage II-33%, III-34%, IV-33%), mean (SD) age 65 (9) years, 57% male and 23 age-matched healthy controls. $USRF_{CSA}$ was significantly reduced (517mm^2 vs 626mm^2; p=0.005) in Stage II patients compared to controls. $USRF_{CSA}$ was also significantly reduced in stage III (500mm^2; p=0.0006) and IV (522mm^2; p=0.007) disease. Using a stepwise regression model in all patients, FEV_1% predicted and $USRF_{CSA}$, but not FFM index and QMVC, correlated with daily physical activity (steps) (r^2=0.4, $p<0.0001$).

Conclusion: $USRF_{CSA}$ is reduced in GOLD stage II COPD and is related to daily physical activity. $USRF_{CSA}$ provides a bedside method for identifying quadriceps muscle loss in less severe disease and may guide the application of pulmonary rehabilitation in these patients.

1. Seymour JM *et al*, Thorax 2009;64:418-23.
2. Seymour JM *et al*, Eur Resp J 2010;36:81-8.

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Does venous blood gas analysis provide accurate estimates of hemoglobin oxygen affinity?

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Background: Polycythemia occurs in conditions with chronic hypoxemia including lung and heart disease, polycythemia vera, hemoglobinopathies and in certain neoplasms. Arterial blood gas analysis and assessment of hemoglobin oxygen affinity by the PO2 with oxygen saturation of 50% (P50) are used to evaluate potential causes of secondary polycythemia. We investigated accuracy of a simplified estimation of P50 from venous blood in comparison to tonometry, the gold standard for measurement of P50.

Methods: In 50 patients referred for evaluation of polycythemia pH, PO2 and SO2 were measured in venous blood (ABL 700 series, Radiometer, Copenhagen) and P50v was derived by standard equations (Severinghaus, J Appl Physiol 1979;46:599). Tonometry was performed to obtain P50t (Hemoxanalyzer, TCS, New Hope, PA). Agreement of P50v and P50t was analyzed.

Results: The mean P50t was 25.8 (range 17.4-34.1) mmHg. The mean difference (bias) of P50v and P50t was 0.5 mmHg, the limits of agreement (95% CI) were -5.15 to +6.09 mmHg. The sensitivity and specificity of P50v to identify patients with P50t outside the normal range (23-27 mmHg) were 5 and 77%, respectively.

Conclusions: Estimates of P50 based on venous blood gas analysis and standard equations have a low bias compared to tonometry. However, the precision of P50v

is not sufficiently high to replace P50t in the evaluation of individual patients with suspected disturbances of hemoglobin oxygen affinity.