204. Modern clinical physiology: imaging structure and evaluating function

1652

In-vivo microscopy of the effect of surfactant on alveolar morphology

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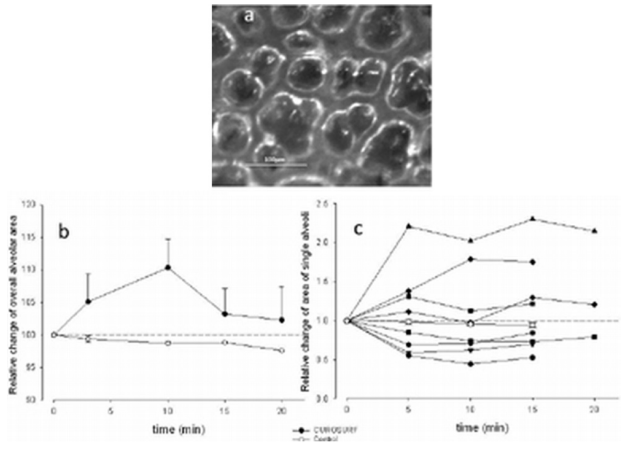
Changes in alveolar morphology induced by intra-tracheal delivery of CUROSURF (CS, Chiesi) were evaluated after opening a pleural window allowing in-vivo microscopic imaging (x300) of sub-pleural alveoli (fig 1a) revealing in physiological, non surfactant deprived conditions, a remarkable degree of geometrical inhomogeneity. Data were collected in 7 male anesthetized, tracheotomized and mechanically ventilated rabbits (0,75-1 kg) who received intra-tracheal instillation of 300 µl, corresponding to 16 mg/kg, of CS.

Images were acquired up to 20 minutes after instillation. Each acquisition (10 images/second) was triggered during the expiratory phase. After defining a ROI (Region Of Interest), alveolar morphology was analized through an image processing program (ImageJ).

Surfactant instillation, on average, caused an increase in alveolar area (fig 1b, closed circles), peaking at about 10% after 10 minutes and returning towards baseline after 20 minutes. The large standard deviation reflects the variability in caliber following CS instillation as shown for individual alveoli in one representative animal (fig 1c, closed symbols). No changes in alveolar geometry were observed in animals not receiving CS (open circles).



Data suggest that CS instillation favors gas diffusion by increasing alveolar surface area, despite a large inhomogeneity in alveolar distension, likely reflecting local differences in surfactant distribution and/or alveolar compliance.

1653

Comparison of changes in the expiratory capnogram waveform and regional ventilation distribution measured by synchrotron imaging during acute bronchoconstriction in brown Norway rat

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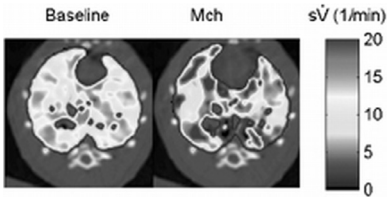
Rationale: Although the increase in the phase III slope of the volumetric expiratory capnogram (S3v) is attributed to ventilation heterogeneity in patients, the relation between S3v and direct measurements of ventilation distribution has not been studied.

Methods: Rats divided into 2 groups: ovalbumin-sensitized (OVA) and exposed to air or to NO_2, 10 ppm, 6h/d, 5d/wk for 4 weeks underwent K-edge subtraction synchrotron imaging, to measure regional ventilation (sV*), the area of well-ventilation regions (VAA) and ventilation heterogeneity (CV of sV*) at baseline and during intravenous infusion of methacholine (MCH, 15 µg/kg/min (γ)). S3v was computed using a rapid CO2 analyzer.

Results: S3v and CV of sV* increased during MCH infusion and the 2 parameters were correlated (R=0.78, $p<0.001$).

m±SD	Air-OVA (n=4)		NO2-OVA (n=4)	
	Baseline	MCH15γ	Baseline	MCH15γ
CV of sV* (%)	15.3±5.2	42.6±25.0*	18.2±8.0	49.3±42.4*
VAA (% Total Lung Area)	93.8±2.5	66.7±22.1*	90.8±7.7	72.3±25.1*
S3v (mmHg/ml)	2.45±0.07	3.32±0.46	2.49±0.15	4.33±0.44*#

*p<0.05 vs. baseline, within a group; #p<0.05 vs. Air-OVA, within a condition, by ANOVA.



Conclusions: This is the first comparison of S3v with direct measurements of ventilation heterogeneity confirming the contribution of this parameter to the increase in S3v during bronchoconstriction.

1654

Within-breath femoral venous blood flow modulation

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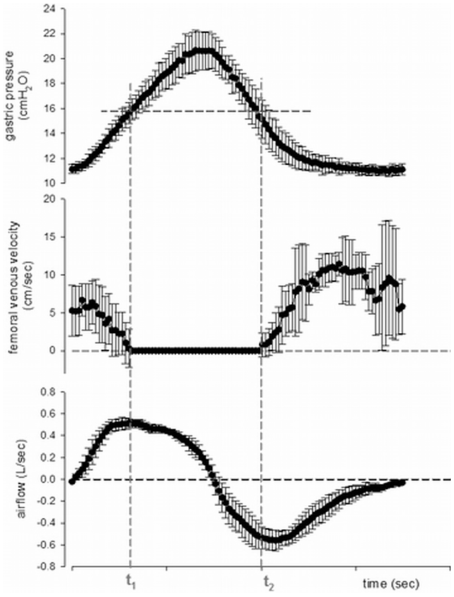
Breathing has a large effect on venous return and abdominal pressure (Pab) varia-



tions can cause the interruption of femoral venous flow (Qfv). The purpose of this study was to determine the values of Pab, airflow, volume and time at which Qfv ceases and restarts within the respiratory cycle time (T_{tot}).
In 4 healthy subjects (age 45±22.1 yr) lying in semirecumbent position airflow was measured during quiet breathing (QB) by a pneumotachograph, Pab by gastric pressure measurements using catheter-balloon-transducer system and Qfv by an echo-Doppler probe. Qfv contour was extracted from the images recorded by the echo-Doppler. The values of Pab, airflow, volume above FRC (ΔV) and times t_1 and t_2 at which Qfv stopped and restarted (where femoral venous velocity could no longer be detected and became measurable again) within T_{tot} were calculated (see figure for a representative case).
t_1 and t_2 occurred respectively during inspiration and expiration when airflow averaged 0.40±0.04 and -0.39±0.10 L/sec. No significant difference between Pab at t_1 (3.1±2.3 cmH_2O) and t_2 (2.8±2.0 cmH_2O) was found. ΔV was 0.33±0.09 at t_1 and 0.48±0.10 L at t_2 ($p<0.05$). The fraction of T_{tot} in which Qfv was negligible, defined as $(t_2-t_1)/T_{tot}$ averaged 0.33±0.07.
These data suggest that during QB Pab variations produced by diaphragm contraction have a profound modulatory within-breath effect on venous return from the lower limb and this modulation is dependent on Pab dynamics.

1655

Pulmonary edema is frequently triggered by marathon running

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Despite the mounting evidence that pulmonary edema can be triggered by strenuous exercise, (Acta Physiol, 2007, 189: 305-17) it is still widely debated (J Appl Physiol, 2010, 109: 1276-80). The purpose of this study was therefore to determine if pulmonary edema is triggered by marathon running and, if so, to examine its incidence and severity. Twenty-seven runners completed the 2011 Steamtown Marathon, in Scranton, PA, United States, beginning at an elevation of 452 meters above sea level (8°C, 96% RH) and ending with a net elevation drop of 291 meters at the finish (21°C, 51% RH). All runners finished between 142 and 289 minutes. Posteroanterior (PA) and lateral (LA) radiographs were taken one day before the race (pre), and then at 19 (SD 8), 55 (13), and 98 (15) min post-marathon finish, the delay ensuring that any post-exercise increase in capillary blood volume would return to normal. Two experienced chest image readers (EM, MP) independently interpreted the images. They were blinded as to the times at which the radiographs were taken. The PA+LA radiographs were viewed together as a set at each time-point and were scored on eight different radiological characteristics. When summed together, the scores could range from 0 (no edema) to 32 (severe interstitial edema). Mean edema scores from all subjects increased from 1.5 units pre-exercise to 4.1, 3.7, and 2.8 units at 19, 55, and 98 minutes post-exercise, respectively ($p<0.01$). Nine runners (33%) had an average increase in the edema score (average of the 19 min post-score minus the average of the pre-score) by 7.1 units (5-fold increase), which still remained high at 55 min post-exercise. In conclusion, pulmonary edema is triggered in 33% of marathon finishers.

1656

Phrenic neuropathy: A missed issue in chronic obstructive pulmonary disease

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Diaphragmatic weakness in chronic obstructive pulmonary disease (COPD) is ascribed to hyperinflation-induced diaphragm shortening as well as impairment in cellular and subcellular structures.1 Although phrenic neuropathy is known to cause diaphragmatic weakness,2 phrenic neuropathy was not previously considered in COPD patients.
Objective: This work aimed at assessing phrenic nerve conduction in COPD patients and its relation to radiographic hyperinflation and pulmonary function.
Methods: Twenty COPD patients were evaluated. Radiographic measures of hyperinflation included diaphragmatic angle of depression (DAOD), lung height, lung width, heart size, and diaphragm level. Flow volume loop parameters were obtained from all patients. Phrenic nerves were transcutaneously stimulated in the neck and diaphragmatic potentials were recorded at xiphoid process and ipsilateral 7th intercostal space. Fifteen healthy subjects were enrolled as controls.
Results: Terminal latency of diaphragmatic potential was significantly prolonged in patients compared to controls (P=0.006 & 0.005 for right and left sides). Phrenic neuropathy was found in 9 patients (45%). Electrophysiological measures of phrenic neuropathy correlated with DAOD on lateral chest film (r=-0.75, P=0.02) as well as with lung height (r=0.67, P=0.003); however they did not correlate with the flow volume loop data.
Conclusion: Phrenic neuropathy is an appreciated finding in COPD patients. Diaphragmatic descend secondary to hyperinflation would induce stretch neuropathy of the phrenic nerve that can negatively affect diaphragmatic function.
References:
[1] Ottenheijm CA et al. Am J Respir Crit Care Med. 2007;175(12):1233-40.
[2] Wilcox PG, Pardy RL. Lung 1989;167:323-41.

1657

Regional hyperinflation in COPD patients: Correlation between lobar hyperinflation and internal flow distribution

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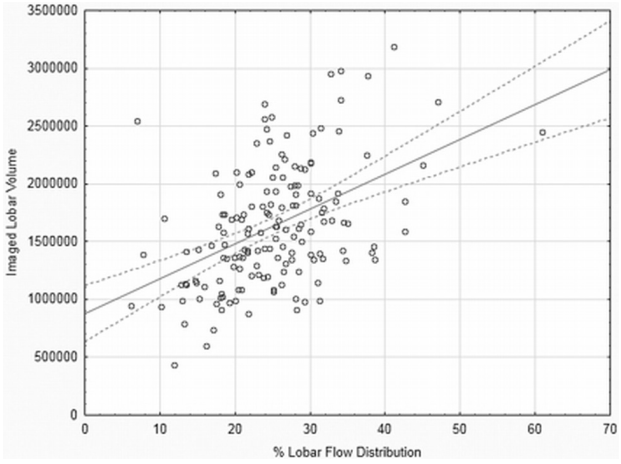
Background: Diagnosis of COPD patients is mainly based on lung function tests. Severe COPD patients often develop dynamic and static hyperinflation. However, few studies have addressed the association of hyperinflation and internal flow redistribution. This study describes the relation between regional hyperinflation and flow distribution in COPD patients.
Methods: Lobar volume levels in COPD patients (n=39, <FEV1> = 42.1±2.1%pred) were determined using functional imaging based on CT data (De Backer J. et al, Radiology 2010; 257(3):854-862). Lobar flow distribution was obtained by calculating the relative difference in the TLC and FRC volumes on the lobar level. The flow distribution towards the different lobes was compared to the imaged based volumes of the corresponding lobes.
Results: Statistically significant correlations (R= 0.4, p< 0.04) were observed between lobar flow distribution and lobar volume-hyperinflation with more flow going to more hyperinflated areas.



Conclusion: Internal flow is redistributed towards the hyperinflated zones which means that also inhaled medication would mainly go to the hyperinflation areas leaving other areas partially untreated and this may further enhance the observed flow redistribution.

1658

Residual lung volume is associated with increased left ventricular mass

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Increased left ventricular (LV) mass and chronic obstructive pulmonary disease (COPD) predict cardiovascular (CV) events, but their relationship is poorly understood. We hypothesized that residual volume would be associated with increased LV mass.
We recruited participants ages 50–79 years with ≥10 pack-year smoking history that were free of clinically apparent CV disease. LV mass was estimated by cardiac magnetic resonance. Body plethysmography and pre- and post-bronchodilator spirometry were performed according to ATS/ERS guidelines. Percent emphysema-like lung was estimated on full-lung CT. Anthropometry, medication use, blood pressure (BP), fasting glucose and lipid levels were measured in a standardized fashion. COPD was defined according to GOLD criteria. Multiple linear regression was used to adjust for age, sex, race-ethnicity, height, weight, body surface area term, smoking status, pack-years, systolic BP, BP meds, fasting glucose, diabetes meds, low density lipoprotein, lipid lowering meds, and percent emphysema.
Of 119 participants completing all study components, 65% had COPD (24% mild, 29% moderate, and 12% severe/very severe). Mean LV mass was 122±34 grams.

Residual lung volume was independently associated with increased LV mass in the fully adjusted model ($p<0.001$). The magnitude of association for residual volume was similar on a SD basis to that of systolic BP (8.7 gm 95%CI 4.5-13 gm per 714 ml increase in residual volume versus 6.9 gm 95%CI 3.5-10 gm per 16 mmHg increase in systolic BP, respectively).
Residual volume is associated with increased LV mass. Further understanding of this relationship may improve cardiovascular risk assessment and represent a novel therapeutic target.

1659

Evidence of impaired spontaneous baroreceptor sensitivity in patients with COPD as a potential link to cardiovascular morbidity and mortality

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Objectives: Recent studies suggest reduced cardiac filling pressures in patients with COPD due to hyperinflation. A reduction in cardiac preload may result in unloading of baroreceptors. We thus investigated spontaneous baroreceptor sensitivity, an independent predictor of cardiovascular morbidity and mortality, in patients with COPD and controls.
Methods: 33 patients with severe airflow obstruction but free from clinical cardiovascular disease (age 64±7yrs, BMI 23±4 kg/sqm, FEV1 27±7%, TLC 140±19%) and 12 age, gender, and body-weight matched controls without airflow obstruction were studied. Spontaneous baroreceptor activity was measured using the sequence method during resting conditions. The baroreceptor effectiveness index was calculated from the total number of baroreceptor sequences divided by the total number of systolic blood pressure ramps.
Results: The mean slope of spontaneous baroreceptor sequences (7.0±4.7msec/mmHg vs. 13.5±6.4msec/mmHg, $p<0.01$) and the baroreceptor effectiveness index (71±54 vs. 103±34, $p<0.05$) were significantly lower in patients with COPD than controls. There was a significant inverse relationship between the slope of baroreceptor sensitivity ($r = -0.302$, $p < 0.05$) and baroreceptor effectiveness index ($r = - 0.391$, $p < 0.01$) with RV/TLC ratio. There were no such associations with airflow obstruction.
Conclusions: Our findings indicate a link between hyperinflation and baroreceptor function in patients with COPD.