56. Pathophysiological mechanisms in disease: new insights

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NT-proANP and lung diffusion in sarcoidosis

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Background: Since that several lines of evidences support a role in modulating pulmonary circulation for the natriuretic peptides, we aimed to investigate possible relationship between NT-proAtrial (NT-proANP) and NT-proBrain (NT-proBNP) natriuretic peptides and lung diffusion abnormalities, as assessed by lung diffusion for carbon monoxide (DL_{CO}), in patients with pulmonary sarcoidosis.
Methods: Resting NT-proBNP and NT-proANP were determined in thirty-two outpatients with pulmonary sarcoidosis, subdivided in two subgroups according to a cut-off DL_{CO} values equal to 75%, and eighteen well-matched healthy volunteers. Each subject underwent, besides pulmonary lung function test, Doppler echocardiographic examination with Tissue Doppler Imaging analysis and cardiopulmonary exercise test.
Results: NT-proANP levels were significantly higher in patients with $DL_{CO} < 75\%$ (2092±768 fmol/L) with respect to those with $DL_{CO} \geq 75\%$ (1575±488 fmol/mL) and healthy subjects (1387±237 fmol/mL) whereas no difference was found for NT-proBNP. A significant univariate relationship was found between NT-proANP and age (r:0.403, p=0.022), DL_{CO} (r:-0.540, p=0.001), specific membrane diffusion capacity (r:-0.480; p=0.006), peak oxygen upatake (r:-0.386, p=0.023), and ventilator efficiency (r:0.431, p=0.011). DL_{CO} was the only variable independently associated with NT-proANP levels at multivariable analysis (β:-0.464; standard error:0.03; p=0.009).
Conclusions: Our findings support a key role of NT-proANP into mechanisms underlying modulation of lung function. The NT-proANP release specifically oriented to counterbalance the lung diffusion impairment is a stimulating hypothesis which warrants confirmation.

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Hydrogen peroxide in exhaled air: A source of error, a paradox and its resolution

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Background: The concentration of hydrogen peroxide (H_2O_2) in exhaled air has been reported to be elevated in asthma and COPD, but the data are inconsistent and difficult to reproduce. Notably, a relevant concentration of H_2O_2 can be found in ambient air. Therefore, we examined the association between H_2O_2 in ambient and exhaled air.
Methods: Exhaled breath condensate (EBC) of 12 COPD patients and 9 healthy subjects was collected with an inhalation filter (F; efficiency 81%) or without (nF). Ambient air condensate (AAC) was collected in parallel and all samples were analysed for H_2O_2. Additionally, ambient H_2O_2 concentration was recorded by an analyser for atmospheric H_2O_2.
Results: H_2O_2 concentration in AAC (3.60±1.40μM, mean±SD) was higher ($p<0.01$) than in EBC (Table). It showed meteorological variations concordant with atmospheric measurements. In both groups studied, the inhalation filter caused a reduction of H_2O_2 values ($p<0.01$). Despite the comparatively low levels in exhaled air, analysis by means of a mathematical model revealed an endogenous H_2O_2 contribution which was more pronounced when using the inhalation filter.

Median (interquartile range), μM	COPD	Control
Exhaled F	0.42 (0.13)	0.45 (0.22)
Exhaled nF	0.78 (0.51)	0.75 (0.32)
Endog. (mucosa conc. equivalent)	0.66 (1.90)	0.69 (3.40)

Conclusion: The paradox of low H_2O_2 values in exhaled air assessed by EBC dissolves when taking into account the reconditioning of inhaled air containing H_2O_2. This may partially explain the heterogeneity of study results and their limited reproducibility. Still, there seems to be endogenous H_2O_2 production but its valid determination requires inhalation filters. This suggests a reanalysis of studies from the literature.

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Effects of abdominal binding on chest wall kinematics in tetraplegic individuals

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Introduction: Tetraplegic individuals show a paradoxical inward motion of the ribcage during inspiration. Abdominal binding is supposed to decrease paradoxical breathing by decreasing abdominal compliance and increasing the zone of apposition of the diaphragm. We hypothesized that abdominal binding would reduce the paradox during quiet breathing (QB) as well as during different levels of hyperpnoea (HYP) and increase maximal voluntary ventilation (MVV).
Methods: Chest wall kinematics were assessed by optoelectronic plethysmography in three male complete tetraplegics (C4-C7) during QB and during HYP at 40 and 100% MVV with and without abdominal binding. Tidal volume (V_T) was partitioned into the relative contribution of the pulmonary rib cage (ΔV_{RCP}), abdominal rib cage (ΔV_{RCA}), and abdomen (ΔV_{AB}). Inspiratory paradox time (IPT) was calculated as the percentage of inspiratory time (T_I) with a decrease in V_{RCP} and/or V_{RCA}.
Results: Abdominal binding reduced IPT at all ventilatory levels. The reduction was higher in RCA than in RCP. At rest, abdominal binding increased ΔV_{RCA} more effectively than ΔV_{RCP}. MVV was larger with abdominal binding in all subjects (105.1±49.0 vs. 92.0±53.9 l min^{-1} without abdominal binding).

	abdominal binding	IPT [%T_I] RCP	IPT [%T_I] RCA	ΔV [%V_T] RCP	ΔV [%V_T] RCA	ΔV [%V_T] AB
QB	without	48 ± 25	59 ± 23	2 ± 10	-2 ± 6	100 ± 15
	with	34 ± 31	21 ± 32	11 ± 10	14 ± 11	76 ± 21
HYP at 40% MVV	without	10 ± 18	31 ± 27	40 ± 24	8 ± 11	52 ± 34
	with	10 ± 17	16 ± 23	35 ± 32	8 ± 14	57 ± 44
HYP at 100% MVV	without	3 ± 5	34 ± 10	64 ± 20	5 ± 6	31 ± 23
	with	0 ± 0	16 ± 6	63 ± 9	13 ± 9	24 ± 18

mean ± SD

Conclusion: The reduction in IPT and the increase in MVV in tetraplegic individuals suggest a functional benefit of abdominal binding which is mainly seen in the lower rib cage (RCA).
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Comparison of measures of ventilation heterogeneity derived from multiple breath inert gas washout

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Introduction: Multiple breath inert gas washout (MBW) is a technique for quantifying ventilation heterogeneity (VH). We compared four measures of VH with regard to repeatability, ability to discriminate between healthy subjects and patients with asthma, and robustness to variations in tidal volume (Vt), anatomical dead space (Vd) and functional residual capacity (FRC).
Methods: MBW was performed in triplicate on 13 healthy subjects and 22 patients with moderate to severe asthma, using a previously published method (Horsley *et al. Thorax*. 2008; 63(2): 135-140). Lung clearance index (LCI), mixing ratio (MiR) and moment ratio (MoR) were calculated. A novel marker of VH, the rate constant ratio (RCR), was calculated by fitting the washout data to a two-phase decay model and calculating the ratio between the fast and slow rate constants. Repeatability and discriminatory ability were assessed using intraclass correlation coefficients (ICC) and receiver operating characteristic (ROC) curves, respectively. Robustness of the parameters was assessed by calculating the signal-to-noise ratio (SNR), using simulated MBW data to determine the noise caused by variations in FRC, Vt and Vd.
Results: LCI, MoR and MiR exhibited good repeatability, with ICC values of 0.899, 0.888 and 0.885 respectively, but RCR was less repeatable (ICC = 0.783). The parameters all had areas under the ROC curve between 0.7 and 0.75. The most robust parameter was the RCR (SNR = ∞), followed by the MiR (SNR = 6.8), LCI (SNR = 3.4) and MoR (SNR = 1.2).
Conclusion: MiR appears to be the most favourable measure of VH. We recommend that it is reported alongside the LCI.

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The role of forced partial expiratory flows to test the bronchodilator response in COPD

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Lung distension (↑FRC) and air trapping (↑RV) are associated with airflow obstruction in COPD patients. Distal obstruction can be assessed by the measurement of forced expiratory partial flows (PF) at low lung volume, 800ml above residual volume, RV, (PF800). The acute effects of salbutamol were evaluated using the Peripheral Obstruction Index (POI), the ratio of RV to PF800. POI can be regarded as a time constant for emptying the lung periphery and has a unit of second.
Methods: Eighty nine COPD subjects underwent measurement of FVC,FRC, RV, PF800 and FEV1 before and after inhalation of 400mcg of salbutamol (BD). PF800 was acquired in a body plethysmograph: after 30 seconds of steady tidal breathing, the patient expired maximally to RV starting from a normal inspiratory tidal volume. (Exp'Air Medisoft Be). Full maximal expiratory manoeuvres were performed after PF800.
Results: Prebronchodilator POI values ranged from 2-60s. POI decreased in 69/89 patients including 19 patients with increases in PF800 but no decrease in RV. The mean decrease in POI was 21%. Of the 50 subjects with decreases in POI and RV, only 26 had increases in FEV1 (>0.2L) and only 35 increases in FVC (>0.2L). Among the 31 patients who increased their RV (mean ± SE: 0,35±0,33 l) after the challenge, only 2 increased their FEV1 whereas 12 increased POI. This suggests a release of pneumoconstriction (Dautrebande 1948) associated with peripheral bronchodilation.
Conclusion: POI appears to be more sensitive than FEV1 for reflecting air trapping and peripheral obstruction. The manoeuvre is less tiring than the maximal forced expiration. The clinical significance of changes in POI remains to be studied.

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Non-invasive detection of diaphragmatic weakness in acid maltase deficiency (AMD)

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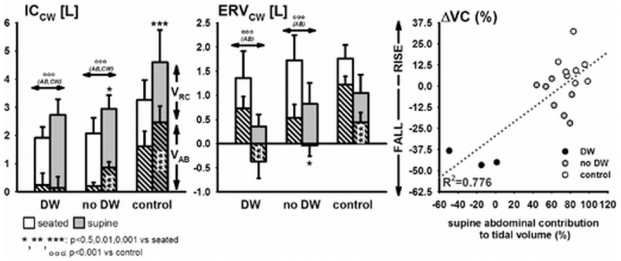
Patients with AMD, a glycogen storage disease resulting in loss of skeletal muscle function, become ventilator dependent when respiratory muscles, particularly the diaphragm, are significantly involved. To identify predictive factors of diaphragmatic weakness in AMD, we studied 10 untreated AMD patients and 8 healthy controls. Supine postural drop of vital capacity (ΔVC) was measured by spirometry, while rib cage (RC) and abdominal (AB) volume variations by opto-electronic plethysmography during quite breathing and slow vital capacity in seated and supine posture. RC and AB contributions to tidal volume (V_T), inspiratory capacity (IC) and expiratory reserve volume (ERV) were derived. Diaphragmatic weakness, defined as ΔVC>25% (Fromageot et al,2001), was present in 3 patients (DW). Posture had a significant effect on IC and AB volume changes during IC and ERV (left and central panel) in controls and patients without DW (noDW). Conversely, in DW patients IC and AB volume changes during IC did not vary with posture, while AB contribute paradoxically (negative values) to ERV in supine position. DW patients also showed negative (i.e., paradoxical inward movement) AB contribution to V_T which correlated with ΔVC (right panel). AB volume variations in both DW and noDW patients were generally lower than controls.



In conclusion, abdominal displacement during V_T and VC maneuver is a good indicator of diaphragmatic weakness in AMD.

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Effect of pulmonary rehabilitation on dynamic hyperinflation according to the BODE index

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Background: The increase of dynamic hyperinflation (DH) is one of the most important causes of exercise intolerance in COPD patient.

Objective: The aim of this study was to evaluate the effects of pulmonary rehabilitation (PR) on dynamic hyperinflation, according to the BODE index.
Method: Prospective study has been conducted; 74 COPD patients have been included for a four weeks period of PR program. Inspiratory capacity (IC) was measured to evaluate DH, at rest and at the end of training session, at the beginning and the end of the PR.
Results: Regardless to BODE index stage, a significant improvement of 7%, 17%, 14% in IC has been observed in all patients at rest, with training on cycloergometer and on treadmill respectively. No significant difference has been found in IC change between quartiles. IC was significantly improved with exercise regarding BODE index quartiles of the according to the type of activity: with exercise on cycloergometer in the quartile II (26%), on treadmill in the quartile IV (47%).
Conclusion: The PR significantly improved the DH in COPD patients regardless to the BODE index. However, no significant difference could be observed in IC change according to the quartiles of BODE index.

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A six months low intensity home-based walking program prevents respiratory muscle impairment in dialysis patients: The EXCITE study
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Changes of lung function in dialysis patients are well known, particularly a progressive deterioration of vital capacity which could be due to respiratory muscles weakness. Regular exercise improves physical capacity in these patients (Heiwe, 2011) with poorly described effects on lung function.
Aim: To evaluate the effect of regular low intensity exercise on lung function and respiratory muscle strength (MIP) in dialysis patients enrolled in a 6-month exercise program prescribed at hospital and performed at home.
Methods: 42 patients (14 F, age 64.3±13) were recruited and divided in 2 groups: prescribed exercise (E = 20), performing every second day two 10-min walking sessions at intensity below the self –selected speed maintained at home by a metronome, and control (C = 22) i.e. well matched dialysis patients who did not enter the exercise program. Physical performance was assessed by the 6- minute walking distance (6MWD), spirometry was measured by Spiropalm (COSMED, Italy) and MIP by MicroRPM (Carefusion, USA). A progressive deterioration of MIP was observed in C. Remarkably, no such deterioration was observed in E.
Results: See Table 1.

Table 1

Mean ± SE	E		C	
	pre	post (+6 months)	pre	post (+6 months)
FVC L (%)	2.8±0.1 (90)	2.7±0.1 (85)	2.8±0.2 (89)	2.5±0.2 (81)
FEV1 L (%)	2.2±0.1 (93)	2.2±0.1 (93)	2.3±0.2 (93)	2.1±0.2 (88)
MIP kPa	7.9±0.6	8.2±0.6	7.7±0.5	7.2±0.5*
6MWD m	343±18	390±23**	334±23	325±22

**p<0.01, *p<0.05.

Conclusions: In dialysis patients a 6-month home walking program improves physical capacity with no changes in spirometry and may prevent progressive deterioration of respiratory muscle function which is observed in the C group.

P250
Impact of a patent foramen ovale (PFO) presence in patients with GOLD stage II chronic obstructive pulmonary disease (COPD)
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Background: A higher prevalence of PFO in COPD has been reported suggesting that PFO may contribute to hypoxaemia and impact exercise tolerance.
Aims and objectives: Our study aimed to evaluate the presence and the amount of right to left shunt in COPD patients with PFO, and to ascertain the impact on resting arterial oxygen and on exercise tolerance.
Methods: 15 GOLD II COPD subjects (8M/7F; Age 69*m*7SD) underwent lung function tests, blood gas analysis and 6' Walk Test (6MWT). Transcranial Doppler (TCD) with the injection of agitated saline at rest and during Valsalva maneuver was performed to evaluate the presence of PFO. 13 subjects completed cardiopulmonary cycle exercise test with breath-by-breath analysis. During the test oesophageal and gastric pressures were measured, and agitated saline injections performed every 2 minutes while TCD signal was recorded.
Results: Seven out of 15 subjects had PFO. PFO+ subjects tended to be slightly more hypoxic than PFO- (PFO+ PaO2 vs PFO- PaO2 77±7 vs 84±6 mmHg, p=0.064) but significant differences between the 2 groups in terms of age, FEV1 and TLco were observed. No significant differences were observed in terms of 6MWT distance, Oxygen Uptake %pred, and MaxLoad %pred. A slight increase in right to left shunting was observed during exercise in PFO+ subjects (rest injection 5±6 bubbles; 2nd injection 10±14; 3rd injection 10±14; 4th injection 11±10). No bubbles were detected during exercise in PFO- patients.
Conclusions: PFO is common in GOLD II COPD. However PFO does not influence oxygen levels at rest or exercise tolerance despite a slightly increased right to left shunt.

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Intensive physical training reduces the airway response to methacholine in asthmatics
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We previously reported that responsiveness to methacholine (Mch) in the absence of deep inspiration (DI) can decrease in healthy subjects after exercise training. We assessed whether exercise training also reduces airway responsiveness in asthmatics. Nine patients (M/F: 3/6; mean age±SD: 24±2 yrs) with mild asthma (FEV1 100±7.4% pred, FEV1/VC 90±6.5%) underwent single dose Mch bronchoprovocations in the absence of DI at baseline (Visit 1) and after training (6 hours/week of submaximal rowing) for 5 (Visit 2) and 10 (Visit 3) consecutive weeks. The single dose Mch was established at Visit 1 as the dose able to induce at least 15% reduction in IVC. The same single dose Mch was administered to each subject at every subsequent challenge. Five asthmatics (M/F: 1/4; mean age±SD: 26±3 yrs) with similar baseline lung function (FEV1: 102±7.0% pred, and FEV1/VC: 83±6.0%; p=0.57 and p=0.06, respectively) not participating to the training program, served as controls (single-dose, no-DI, Mch tests at baseline and 10 weeks). In the trained group, the Mch-induced reduction in IVC from baseline was 22±10% at Visit 1, 13±11% at Visit 2, 11±8% at Visit 3 (ANOVA for repeated measures: p=0.028). Mch responsiveness at Visit 2 and 3 was reduced compared to baseline (p=0.03 and p=0.01, respectively). The reduction in responsiveness induced by training was of magnitude similar to that previously obtained in healthy subjects. In controls, Mch-induced reduction in IVC at baseline was similar to that of the trained asthmatics (21±20%), and remained unchanged after 10 weeks (29±14%, p= 0.28). This pilot study indicates that physical training is capable of reducing airway responsiveness in mild asthmatics.

P252
Effects of long and short acting β_2-agonists on respiratory muscles during hypercapnia
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Both short acting Salbutamol (Salb) and long acting Sameterol (Salm) β_2-agonists are widely used bronchodilators. Both significantly increase sniff nasal inspiratory pressure and inspiratory muscle EMG in humans (ERJ P2965,2003, P358s,2005). Do these β_2-agonists exert similar effects on expiratory muscles as on inspiratory muscles, during breathing?
In 8 normal subjects, we inserted electrodes into parasternal intercostals (PARA) and transversus abdominis (TA) muscles using ultrasound.
After baseline measurement, 20μg/min of Salb was administrated continuously in Salb group (n=4):, or 100μg of Salm was inhaled Salm group (n=4). Then, ventilation, as well as PARA and TA EMG were measured during resting and CO_2 stimulated breathing in both groups.
Data was analyzed with and without β_2-agonist in four conditions (room air, $Etco_2$=50 Torr (CO_2Mild), 55 Torr (CO_2Mod) and 60 Torr (CO_2Hi)). Tidal EMG was expressed as percent maximum tidal EMG (%EMG_{max}).
Compared to baseline,
A) with Salb, 1) V_T increased significantly in all conditions, and V_I and f increased significantly in CO_2Mod and CO_2Hi. 2) PARA EMG increased significantly in CO_2Mod and CO_2Hi, 3) TA EMG decreased significantly in CO_2Hi.
B) with Salm, 1) f and V_I increased significantly in CO_2Hi, but V_T did not increase in all conditions, 2) PARA EMG increased significantly in all conditions, 3) TA EMG did not change in all conditions.
We conclude that during resting and CO_2 stimulated breathing β_2-agonists do affect both t inspiratory and expiratory muscles, but there is a different effect on breathing pattern and muscle activation for short versus long acting β_2-agonists.
This study was approved by Kitasato university human ethics committee.

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Comparison of different measurement methods of gas diffusion in the lung

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Background: Lung fibrosis results in decreases of oxygen diffusion and oxygen arterial partial pressure ($P_{a,O2}$) especially during exercise. Obstructive airway diseases are often associated with a mismatch of ventilation and perfusion. We investigated the validity of the CO diffusion capacity ($D_{L,CO}$) in comparison with $P_{a,O2}$ and alveolo-arterial oxygen gradient ($AaDO_2$) in different lung diseases.
Methods: 250 subjects (52.3±12.5 yrs) were examined, out of 206 there were: 13 with VC<LLN (normal FEV_1/VC, $D_{L,CO}$ normal or reduced); 19 with normal VC but $D_{L,CO}$ <LLN; 86 with mild or moderate bronchial obstruction (FEV_1/VC<LLN, VC>LLN), and 88 healthy controls. Pearson correlation coefficient of $D_{L,CO}$ with $P_{a,O2}$ and $AaDO_2$ were analyzed in each group.
Results: $D_{L,CO}$ (%pred.), $P_{a,O2}$ at rest, and $AaDO_2$, respectively, showed low correlation in all groups (0.25**; -0.19*) (**=p<0.001, *=p<0.01). $D_{L,CO}$ and $P_{a,O2}$ during exercise revealed moderate correlation in the group with bronchial obstruction (0.55**), but there were strong correlations in the groups with reduced VC and/or $D_{L,CO}$ (0.82**; 0.68*). Correlations between $D_{L,CO}$ and $AaDO_2$ during exercise were the best in the latter two groups (-0.84**; -0.64*), medium in the group with bronchial obstruction (-0.47**), but not significant in healthy controls (0.19).
Conclusions: Only in patients with reduced VC and/or impaired $D_{L,CO}$ all three parameters are likely to objectify impaired gas exchange in the lungs. $AaDO_2$ relates to the ventilation, this may be the cause of the good correlation with $D_{L,CO}$. In the group with bronchial obstruction $D_{L,CO}$ seems to be influenced by other pathophysiological aspects, resulting in only moderate correlation between the different parameters.

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Asynchronous breathing movements during slow controlled deep inspiration in chronic stroke patients

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Aim: To assess the asynchronous index of respiratory movements during the slow controlled deep inspiration in chronic stroke patient's and healthy subjects.
Methods: Ten chronic stroke patients (experimental group - EG) (53.1±9.2 years) and ten age-matched healthy subjects (control group, CG) (53.6±9.4 years) were studied by Optoelectronic Plethysmography in 3 moments, quite breathing (QB) slow controlled deep inspiration (DeepI,3 series/10 repetitions) and recovery quite breathing (rQB). We measured the phase angle (PhAng), inspiratory phase relation (PhRIB), expiratory phase relation (PhREB) and time of the phase shift between the chest wall compartments.
Results: Both groups were similar during the QB and rQB. During DeepI series we observed a distinct behavior between EG and CG, in series 1 to 3 respectively. Time of the phase shift between the rig cage and abdominal compartments during the DeepI series were 0.23±0.2s *vs.* 0.15±0.11s, 0.22±0.2 *vs*. 0.11±0.1s, 0.21±0.2s *vs.* 0.12±0.1, p= 0.037.

	Experimental group			Control group			
	Serie 1(IS)	Serie 2 (IS)	Serie 3 (IS)	Serie 1 (IS)	Serie 2 (IS)	Serie 3 (IS)	*p*
PhAng	16.7±5.7[a]	17.5±6.5[b]	17.2±6.6[b]	11.5±3.7[a]	10.1±3.9[b]	10.2±4.7[b]	<.0001
PhRIB	15.9±10.1%	17.9±5.5%	17.4±9.2%	10.7±4.6%	11.5±3.5%	10.2±3.4%	.0005
PhREB	18.9±8.6%	16.9±7.5%	17.7±10.3%	9.1±5%	8.9±4.2%	11.2±8.1%	.0001

Conclusion: Slow controlled deep inspiration induces more asynchronous breathing movements in chronic stroke patients than healthy subjects.

P255

Experimental air-hunger inhibits laser-evoked potentials

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Rationale: Counter-irritation is the attenuation of a painful sensation by a newly occurring heterotopic stimulus that must be of noxious nature. Dyspnea-pain counter-irritation has been described with experimental dyspnea of the work/effort type, which inhibits both the spinal nociceptive reflex (about 50% reduction in amplitude) and laser evoked cortical potentials (LEPs, about 35% reduction in amplitude). In contrast, experimental air hunger has no influence the RIII reflex. Its effects on LEPs are unknown.
Methods: LEPs were obtained using a CO2 laser stimulator in twelve healthy naïve subjects (age range = 21-29 years), during eupneic ventilator controlled breathing with a FiCO2 of 0% (VC condition) and after inducing air hunger by increasing FiCO2 at a fixed level of ventilator controlled ventilation (VC-CO2 condition).
Results: Air hunger was intense in the VC-CO2 condition (VAS rating = 6.3±0.6 cm, mean ± SD, $p < 0.05$ vs. VC). Concomitantly, the amplitude of the N2P2 component of the LEPs was reduced in comparison to the VC condition (-22,6% ± 17,8%, p<0,05).
Discussion: Although seemingly to a lesser extent than work/effort dyspnea, air hunger does inhibit LEPs. This contrasts with the lack of inhibition of the spinal nociceptive reflex in response to air hunger, a difference that could be in line with the central components of LEPs and the interaction between pain and air hunger at the cortical level. Air hunger may have some nociceptive characteristics, which could potentially open novel therapeutic avenues acting on central mechanisms.

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Inhibitory conditioning of the supplementary motor area with repetitive transcranial magnetic stimulation inhibits diaphragm motor-evoked potentials in healthy humans

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Rationale: The supplementary motor area (SMA) has functional connections with the diaphragm. Facilitatory conditioning of the SMA using repetitive transcranial magnetic stimulation (rTMS) results in an increased excitability of the corticospinal pathway to the phrenic motoneurones (increased diaphragm motor evoked potentials, DiMEPs). This paves the way for rTMS respiratory applications, e.g. modulate respiratory sensations. However, whether DiMEPs can be inhibited through SMA manipulations is unknown. We stimulated the SMA using continuous theta burst stimulation, an inhibitory rTMS protocol (I-rTMS), and measured DiMEP amplitude.
Methods: Eight naive healthy subjects (age 25±3 years, mean ± SD, 3 men) were studied. DiMEPs (surface electromyogram) were elicited by single-pulse TMS over the diaphragm primary motor area (M1dia). DiMEPs were recorded at baseline and circa 5, 10 and 20 minutes after I-rTMS (post1, post2, and post3, respectively).
Results: I-rTMS over the SMA reduced the amplitude of DiMEPs, from 328±181 μV at baseline, to 239±126 μV, 209±114 μV and 212±123 μV at post 1, post 2 and post 3, respectively ($F_{7,13}$, p<0,005 vs. baseline). These changes were observed in the absence of any reduction in the amplitude of the pre-stimulus EMG ($F_{1,74}$, p>0.05).
Conclusions: Inhibitory theta-burst stimulation of the SMA decreases the excitability of the corticospinal pathway to the phrenic motoneurones. This suggests the existence of a tonic excitatory connection between the SMA and M1dia. The possibility of targeting this connection to interfere with respiratory sensations remains to be determined.

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Acidotic responses in patients with idiopathic pulmonary fibrosis: The mechanisms of exertional dyspnea

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Background and objective: Very often, some idiopathic pulmonary fibrosis (IPF) patients with the severe exertional hypoxemia may realize only mild dyspnea; the mechanisms underlying the exertional dyspnea in such patients have not yet been elucidated. We investigated the exercise responses to hyperoxia in relation to dyspnea profile as well as cardiopulmonary and acidotic parameters in 13 patients with stable IPF.
Methods: This was a single-blind trail, in which subjects breathed 30% O_2 or compressed air (CA) in random order during two incremental treadmill exercise tests.
Results: $Pao_2$and $Paco_2$ were higher during exercise ($p < 0.01$, $p < 0.001$, respectively, by repeated-measures ANOVA). At the peak exercise, 30% O_2 reduced plasma lactate level ($p < 0.05$), and dyspnea score and the mean change from resting condition in pH were similar while breathing 30% $O_2$and CA. The dyspnea-ratio (%) of Doxygen uptake (peak minus resting oxygen uptake) curve reached a break point that occurred at a similar exercise point while breathing 30% O_2 and CA.
Conclusions: Despite inhaling 30% O_2 and CA, IPF patients did not develop ventilatory compensation in exertional acidosis, stopped exercise when the similar changes from resting condition in pH were seen. Furthermore, hyperoxic conditions did not alter the pattern of exertional dyspnea in IPF patients during a standardized exercise program.

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Study of pulmonary function in type2 diabetes mellitus and its changes with change in duration and glycemic control

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Rationale: Diabetes mellitus (DM) is a metabolic disease causing changes in

multiple systems, and pulmonary system is not an exception to this rule. As the prevalence of T2DM is increasing, the potential implication of diabetic status affecting pulmonary system demand attention.
Objectives: To assess the pulmonary function in Type2 DM patients and its variation (if any) with Duration of disease and level of glycemic control.
Methods: A comparative study was conducted including 60 T2DM patients and 60 age and sex matched controls. The special investigations were done: 1. HBA1c, 2. PFT by flow sensitive spirometer 3.DLCO by single breath technique. Grouping of cases were done according to duration of T2DM (Gr.Ia=≤5yr, Gr.Ib=6-10yr, Gr.Ic=>10yr) and HBA1c level (Gr.IIa=<6,Gr.IIb=6-7,Gr.IIc=>7).
Results: Significant changes in PFT parameters and Diffusion capacity-DLCO% and DL/VA% in cases compared to controls.There was significant (P<0.05) decrease in FVC%, DLCO% and DL/VA% & increase in FEV1/FVC% in Gr.Ic and Gr.IIc compared to Gr.Ia & Gr.IIa. There was negative correlation of FVC% (r=-0.53),DLCO% (r=–0.66,) and DL/VA% (r=–0.68) with duration & with HBA1c level- FVC% (r=–0.50), DLCO% (r=–0.65) and DL/VA% (r=–0.62) with HBA1c level where as FEV1/FVC% was positively correlated with duration (r=+0.39) and HBA1c (r=+0.50).
Conclusion: There is significant changes of pulmonary functions with changes in duration and glycemic control, which may be due to non enzymatic glycosylation of tissue proteins and chronic diabetic microangiopathy. So, in routine screening by doing PFT, we can reduce mortality and morbidity of the patients (type2DM) due to subclinical or overt pulmonary dysfunctions.

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Inhibition of voluntary respiratory movements depends on the phase of the respiratory cycle
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Movement inhibition is important, notably for the voluntary control of respiration, as its dysfunction may preclude the execution of important social tasks such as speech. Here we investigate whether the double command involved in respiration (cortical and medullary) has an impact on the inhibitory mechanisms. Specifically, we studied the inhibition properties (baseline, rate, threshold) of voluntary respiratory movements in relation with the phase of the breathing cycle in which the command signal is given.
Subjects were instructed to produce inspiratory movement in response to a visual target. For ∼50% of the trials, a stop signal was presented (a second visual target) in response to which subjects had to inhibit the inspiratory movement. Respiratory movements were measured through abdominal expansion using a magnetometer. Respiratory reaction time (RT) and stop-signal accuracy were used to calculate stop signal reaction time (SSRT), an estimate of the time required to inhibit the respiratory movement.
The results indicate that respiratory RTs depended on the context in which the stop signal was presented, being shorter during inspiration (541±21ms; mean±SD) than expiration (568±29ms). The estimated respiratory SSRT was 299±48ms and 253±27ms for inspiration and expiration, respectively.
These preliminary results suggest that the time required to inhibit respiratory movements (∼270ms) tends to be longer than the times to inhibit ocular movements (visual signal ∼150 ms; auditory signal ∼200 ms). This might either indicate the implication of distinct inhibition centers for these two types of movements or distinct inhibitory processes for oculomotor ballistic or respiratory controlled movement.