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Late-breaking abstract: 5-HT mediates susceptibility of rats with low intrinsic aerobic capacity to hypoxia-induced pulmonary hypertension
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Introduction: Low aerobic exercise capacity has been linked with a higher probability of death. We have previously demonstrated that low exercise capacity rats have increased susceptibility to pulmonary arterial hypertension when subjected to chronic hypoxia. Here we investigate the role of 5-HT in conferring susceptibility.

Methods: We exposed high and low exercise capacity rats to a 10% O2 environment for 21 days, +/- daily treatment with a 5-HT inhibitor (pCPA). The animals, bred over 21 generations for high (HCR) or low (LCR) running capacity, differ by 500%. PAH biomarkers were determined in heart, lung and blood.

Results: LCR rats developed significantly greater PAH pathologies compared to HCR with regard to cardiac and pulmonary vessel remodeling, right ventricular (RV) pressure and echocardiographic measures. Cardiac histology demonstrated pCPA treatment ablated the RV hypertrophic response and myocyte apoptosis in both HCR and LCR animals. 5-HT levels in LCR animals were increased in response to hypoxia, yet unchanged in other groups, and levels in both strains were ablated by pCPA treatment. Although pCPA effected reduction in all PAH pathologies in all groups, subtractive analysis revealed no impact on the enhanced vessel remodeling and only a partial effect on RV pressure observed in LCR animals. RV mass and echocardiographic measures of RV function, however, were fully reversed.

Conclusion: These data support our hypothesis that intrinsically low aerobic capacity may predispose individuals to developing pulmonary arterial hypertension, and that the associated dysregulation of the 5-HT pathway principally impacts RV function rather than vessel remodeling.
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 Spirometric corroboration of radiographic changes suggestive of COPD and influence on ventilation-perfusion scanning

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 Introduction: An abnormal chest radiograph (CXR) can affect the ventilation-perfusion (V/Q) scan interpretation in the investigation of suspected pulmonary embolism (PE). V/Q scans are not always preceded by a normal CXR and many CXRs are reported as showing changes “compatible with COPD.”

 We decided to ascertain whether radiological suspicion was supported by spirometric evidence of COPD and whether those with more severe COPD were more likely to have an intermediate probability V/Q scan.

 Methods: All V/Q scans and CXR reports for the 12 months from February 2008 were analysed. The spirometry database was searched and results obtained.

 Results: 68 patients had V/Q scans and CXRs were reported as showing changes compatible with COPD. 44 (65%) had not had spirometry. Of the 24 (35%) patients with spirometry, 3 reports were unavailable and 19 (90%) were compatible with COPD. The mean FEV1/FVC ratio was 50.7.

 The V/Q scan reports are classified according to COPD severity in the table below.

<table>
<thead>
<tr>
<th>Spirometry</th>
<th>Number (%)</th>
<th>V/Q scan report: Probability of PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No evidence COPD</td>
<td>2 (9%)</td>
<td>Low</td>
</tr>
<tr>
<td>Mild</td>
<td>4 (19%)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Moderate</td>
<td>6 (29%)</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Severe</td>
<td>4 (19%)</td>
<td>High</td>
</tr>
</tbody>
</table>

 Conclusion: Of the 68 patients reported as having radiological “evidence” of COPD, only 24 (35%) had had spirometry. Of the 21 patients with spirometry reports (91%) did not have COPD.

 None of the patients with COPD had an intermediate probability V/Q scan. COPD is often “reported” on a chest radiograph but spirometric evidence is not always present and, if present, does not always confirm the radiological suspicion.

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 Comparative effects of amlodipine and sildenafil on the NT-proBNP levels of patients with COPD-induced pulmonary hypertension

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 Introduction: Pulmonary hypertension (PH) secondary to chronic obstructive pulmonary disease (COPD) is an important cause of death. N-terminal of pro-brain natriuretic peptide (NT-proBNP) has been suggested as a noninvasive marker for the presence and severity of PH. The changes in NT-proBNP concentration correlated with clinical symptoms. Specific treatment of PH in the setting of COPD has not been adequately studied. We assessed oral vasodilators’ (sildenafil and amlodipine) effect on NT-proBNP level in PH due to COPD.

 Methods: Forty clinically-stable patients with the history of COPD who had a normal ejection fraction (EF), NY systolic pressure greater than 45 mmHg and baseline blood NT-proBNP levels above 100pg/ml were enrolled. They were di- vided into two groups. Patients in the first group received sildenafil 50 mg twice daily (group A) and the second group was given amlodipine 2.5-7.5 mg once daily (group B) for 2 weeks. NT-proBNP levels were measured before and after the 2 week drug administration.

 Results: Drug therapy with oral vasodilators (both amiodipine or sildenafil) could significantly reduce NT-proBNP levels in COPD-induced PH patients. Also there were no significant differences between amiodipine and sildenafil in lowering NT-proBNP levels (effectiveness of therapies).

 Conclusion: Drug therapy (oral vasodilators) in COPD-induced significantly decreased NT-proBNP levels in this study. Though, no significant difference between amiodipine and sildenafil in reducing NT-proBNP levels was observed. Changes in NT-proBNP levels could be used as an indicator to mirror the effectiveness of therapies.
vascular remodeling has been observed in all COPD patients. Pathophysiologic findings of COPD could be explained by the effects of alveolar hypoxia, en-
dothelial dysfunction. Endothelin 1 (ET-1) is a vasoactive mediator that causes vasoconstriction and vascular wall proliferation.

The aim of the present study was to investigate systemic endothelial function and some parameters of pulmonary and central circulation in patients with stable moderate and severe COPD. Methods: 20 COPD patients with 2 stage and 22 COPD patients with 3 stage were under consideration. Endothelial function was determined by Celemarjier’s test. This study was performed by time–linked immunosay.

Results: Reduction of endothelin–depending vascular reaction was determined in 16 patients (69%) with COPD: 18 patients were severe and 10 patients were with moderate COPD. There was no difference in vasodilatation endothelin–
dependent reaction at 16 (34%) patients to control with one controls. ET-1 level in plasma of COPD patients with 3 stage was higher (p<0.05) vs. 2 stages patients and healthy control (p<0.01). Linear regression analysis showed direct correlation between ET-1 level and pulmonary artery systolic pressure (rs=0.68). The statistical results mean that ET-1 dysfunction may contribute to increases in pulmonary arterial tone and pulmonary hypertension in COPD.

We conclude: endothelial dysfunction in patients with COPD become intensely from moderate to severe stage, that by-turn influence to increase on central and pulmonary haemodynamics damage.

P2368 Evaluation of left ventricular function in patients with COPD – A mono centric retrospective study

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The functional abnormalities of right ventricle in long standing chronic obstructive pulmonary disease (COPD) have been well documented. Derangement of the right ventricular (RV) function is in the absence of other disorders affecting the LV, has not been clearly established.

This study has been designed to provide more definitive information concerning left ventricular function in patients with COPD primarily to ascertain the involvement of left ventricle in stable COPD patients in whom other sources of diastolic dysfunction has been systematically excluded which the previous studies had failed to do. The aim of the study was to evaluate LV function in COPD patients.

Methods: We selected all COPD patients with and without additional cardiac diseases and 30 age and sex-matched healthy subjects were enrolled into the study. We defined COPD by GOLD criteria. Well Investigated parameters of Left ventricular diastolic functions like E/A (peak velocity of early E wave/Eespeak velocity of early A wave) (transmural flow), IVRT (isovolumetric relaxation time), MPI (Myocardial Performance Index) were used for the evaluation of LV diastolic function.

The study shows that 30% i.e. 9 of the 30 patients admitted to the hospital with COPD had left ventricular diastolic dysfunction and that the risk of association with Left ventricular diastolic dysfunction is 6 times more in COPD patients than that in normal individual.

In COPD patients, LV diastolic function is significantly impaired and its magnitude is related with the severity of COPD as well as the increase in pulmonary artery pressure. This is in spite of preserved LV systolic function.

Drug therapy for pulmonary hypertension associated to chronic lung disease is currently discouraged for the negative effects on gas exchange. We retrospectively analyzed all patients with COPD treated with IVP or COPD during 12 months of treatment with Bosentan or Sildenafil. 22 pts with diagnosis of severe pre-capillary PH at right heart catheterization were evaluated including 10 IPF and 12 pts with COPD. Haemodynamic and long term respira-
tory function data were available in 20 pts: 5 pts with COPD treated with Bosentan, 5pts COPD with Sildenafil, 5 pts IVP treated with ERA and 5 pts with PDE5-inh. Blood gases measuring PaCO2 and PaO2, PFTs and 6MWT were analyzed at baseline, T6 and T12 months. A-aO2 gradient was calculated using alveolar gas equation. Baseline there were not any differences between haemodynamics and gas exchange profile between IVP and COPD (fH=40±2/min vs 44±2/min), PaO2 89±2 vs 57±1 mmHg. PVR decreased by 49% and 77% in IVP and COPD respectively. A-aO2 gradient decreased by 29% and 57% at T6 and T12 respectively in IVP and COPD patients.

Conclusion: We conclude that bosentan is a safe and well tolerated therapy in COPD with severe PH. P2379 Inhalation of a prostacyclin analog (iloprost) does not improve exercise capacity in COPD with disproportional pulmonary hypertension

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Background: Pulmonary hypertension (PH) is a well-recognized complication of COPD. Although it is likely that cardiovascular factors limit exercise capacity in patients with COPD, the potential for pulmonary vasodilator therapy to improve exercise capacity in this population has not been well characterized. The objective of this trial was to investigate whether inhalation iloprost improves exercise capacity in COPD patients with disproportional PH.

Methods: We performed a 6-month, randomized, double-blind, parallel-group study with iloprost treated and placebo treated groups. All patients had COPD of moderate-to-severe severity and pulmonary hypertension associated to IPF or COPD and were women.

Results: Patients had a mean age of 73.2 years±6.7 and FEV1% pred of 51.6%±30.0. The mean PaCO2 was 42.7±8. During the exercise, three patients had severe side-effects, precluding study continuation. The walking distance was
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not significantly affected by treatment (mean Δ [95% CI]: -12.4 mmHg [-32.7 to -7.9] p=0.22). Neither the lowest SaO2 (<94% [2.69 to -0.82], p=0.28) nor the perceived exertion on BORG scale (0.12 [0.58 to 0.82], p=0.73) differed among the groups. However, VO2 max (77.6 mL/min [122.1 to -31.6], p=0.002) and the maximal minute ventilation (2.99 L/min [-4.5 to -1.5], p<0.001) were significantly lower in patients receiving iloprost as compared to placebo.

Conclusions: This study did not report on exercise capacity in patients with COPD and disproportional pulmonary hypertension.

P2371 Pulmonary hypertension and exercise performance in advanced COPD

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Rationale: Pulmonary hypertension is a common occurrence in advanced COPD, but its effects on exercise performance remain unclear.

Aim: To determine the effects of pulmonary hypertension in advanced COP on exercise performance.

Methods: We conducted the exercise testing and the echocardiographic examination in 32 patients with advanced stable COPD. Mean pulmonary artery pressure (mPAP) was calculated from the acceleration time of pulmonary flow. Exercise capacity was evaluated by the distance walked in 6 min (6MWD) and by an incremental cardiopulmonary exercise test (CPET).

Results: The patients had a forced expiratory volume in 1 s (FEV1) of 1.15±0.34 L (40% predicted, range 23±0.5-50%), corresponding to GOLD stages III and IV, and a 6MWD of 310±62 m (mean ± SD). The CPET showed: a maximum workload of 50±22 W, a peak O2 uptake of 12.4±3.4 mL/kg/min, a peak heart rate of 125±18 bpm, a peak respiratory exchange ratio 1.03±0.7, a ventilation VE/CO2 production slope of 34.9±9, and a peak O2 pulse 7.1±1.3 mL. The peak VE was 40±13 L/min, and the calculated maximum voluntary VE 42±18 L/min. There was no significant difference in any of the CPET variables and 6MWD between the patients with a mPAP > 30 mm Hg (mPAP 24±4.5 mm Hg, n=17) and those with a mPAP ≤ 30 mm Hg (mPAP 33±4 mm Hg, n=15). There was no correlation between PAP and any of the exercise measurements.

Conclusions: These results suggest that exercise performance in patients with advanced COPD and mild to moderate pulmonary hypertension is essentially limited by exhaustion of the ventilatory reserve.

P2372 Prevalence of established and exercise induced pulmonary hypertension in COPD

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Aim: To describe prevalence of pre-capillary pulmonary hypertension (PH) and exercise induced pulmonary hypertension (EIPH) in COPD without left sided heart diseases, and to relate PH to GOLD stages II-IV.

Methods: 98 patients, 64.7±9 yrs and 50% men, were recruited. Right heart catheterization and echocardiography was performed in all patients. Throughout the studies, all COPD patients had a forced expiratory volume in 1 s (FEV1) ≤ 2.5 L (40% predicted, range 35-50%), corresponding to GOLD stages III and IV, and a 6MWD of 310±62 m (mean ± SD). EIPH was defined as an increase in mPAP (≥25 mmHg) during exercise. The patients were stratified by GOLD stages II, III and IV, respectively. At rest and at peak exercise PaO2 decreased whereas PaCO2 increased with advancing GOLD stages. At rest, only stage IV had lower (p<0.05) PaO2 in patients with PH than in those without. At peak exercise both stage III and IV had lower (p<0.05) PaO2 in patients with PH than in those without. For PaCO2 no significant differences were observed within each GOLD stage.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>GOLD II</th>
<th>GOLD III</th>
<th>GOLD IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>36</td>
<td>21</td>
<td>15</td>
</tr>
<tr>
<td>PaO2 rest, kPa</td>
<td>10.2±1.0</td>
<td>10.3±0.9</td>
<td>10.1±1.1</td>
</tr>
<tr>
<td>PaCO2, kPa</td>
<td>7.2±0.4</td>
<td>7.1±0.4</td>
<td>7.5±1.5</td>
</tr>
<tr>
<td>6MWD, m</td>
<td>41±4</td>
<td>35±4</td>
<td>32±4</td>
</tr>
</tbody>
</table>

Conclusion: PH was a common finding in advanced COPD. Arterial PaO2 at rest and at peak exercise was inversely related to GOLD stage. Presence of PH within each stage was associated with lower PaO2. Since RHC is not available to all COPD patients, PH is useful in selecting candidates. Low resting PaO2 and excessive decline in PaO2 during exercise justify referral to further PH investigation.

P2374 Experimental hypoxia-induced pulmonary hypertension is prevented by moderate exercise training in mice

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Pulmonary hypertension (PH), a progressive disease of multifactorial etiology, has a poor prognosis and results in right heart dysfunction. PH is characterized by pulmonary vasoconstriction and abnormal vascular remodeling processes. Current medication does not cure the disease; at best disease progression can be mitigated. Main symptoms of PH are fatigue and shortness of breath. Thus, exercise training has been considered as counterproductive in the past. In our study, moderate exercise training prevented pulmonary vascular disease in a mouse model of hypoxia-induced pulmonary hypertension. During 21 days of exposure to hypoxia mice were trained on a treadmill, daily for five days a week. Readouts were maximum walking distance, maximum oxygen uptake (VO2 max), right ventricular systolic pressure (RVSP), measured continuously by telemetry, right ventricular mass in relation to the left ventricle and septum, and small vessel muscularization. Treatment with sildenafil in combination with training improved the maximum walking distance compared to non-trained control mice. Placebo-treated trained mice in hypoxia showed a significant increase of VO2 max, the effect being similar to the pulmonary capillary wedge pressure (PCWP) in untreated trained mice; small vessel muscularization was reduced to a similar degree as with sildenafil-treatment only. Chronic hypoxia induced a significant hypoxia-induced upregulation of PDGFB in whole-tissue-trained control mice. Overall, our data demonstrate the efficacy of exercise training for prevention of hypoxia-induced pulmonary hypertension, which might be mediated by inhibition of PDGF upregulation.

P2375 Biomarkers for pulmonary hypertension in interstitial lung disease

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Pulmonary hypertension (PH) is defined by a mean pulmonary artery pressure (MPAP) >25 mmHg. New patients with ILD are screened by echocardiography to detect signs of PH. This study evaluates NT-proBNP, D-imeric acid and erythrocyte NO as biomarkers in diagnosis of PH in patients with ILD. We included 206 patients with ILD were screened for PH by echocardiography. A tricuspid pressure gradient (TI) ≥ 40 mmHg, dilatation or decreased tricuspid annular plane systolic excursion (TAPSE) indicated PH on echocardiography. If possible, right heart catheterisation (RHC) was performed in patients with PH on echocardiography to confirm the diagnosis. Levels of biomarkers in patients with and without PH on echocardiography, were measured and sensitivity, specificity, negative (NPV) and positive predictive values (PPV) for detection of PH were calculated.

Results (mean±SEM): 30 patients had PH based on echocardiography (TI ≥ 59±3
Left ventricle diastolic dysfunction in severe COPD and exercise tolerance

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COPD patients with similar airflow obstruction could have different degree of dyspnea and exercise tolerance. Actually it is unknown why this happens. The aim of our study was to evaluate the prevalence of left ventricle diastolic dysfunction (LVDD) in stable severe COPD patients, analyzing its implication in exercise tolerance and the relationship with specific functional and analytical parameters.

Methods: We evaluated 75 consecutive outpatients with FEV1 between 30-50%. Twenty five (33%) were excluded because of previous heart disease, atrial fibrillation or Charlson score > 5. Pulmonary function test, 6-minute walking test (6MWT), arterial gases, Nt-proBNP, inflammatory markers (CRP, leukocytes) and echocardiographic DD parameters were performed in all patients.

Results: Patients were 67±4 y/o, 92% men, tobacco consumption 58±24 p/y. Prevalence of risk factors was: hypertension 44%, DM 26% and dyslipidemia 32%. The functional data showed: FEV1 39±5%, FVC 76±16%, TLC 129±24%, RV 228±87%, PaO2 67±10, BMI 28±5, dyspnea MRC scale I-II (72%) and III (28%), 6MWT distance 367±87 m, BODE between 2-7.

LVDD prevalence was 98% (type I 85%, type II 15%). No relationship was found between 6MWT distance or dyspnea and DD parameters (E/A ratio, pulmonary vein flow, E/E' ratio), hyperinflation or laboratory tests. LVDD did not correlate to hyperinflation, inflammation or right ventricle overload.

Conclusions: Prevalence of LVDD in severe COPD patients is very high however it does not seem this condition determines their exercise tolerance. In our study, high prevalence of LVDD is not related to air trapping, inflammation or interventricular dependence so other factors should be studied.

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