403. Pulmonary circulation: clinical end-points and clinical physiology

P3916

Assessment of tissue velocity imaging of both ventricules in vasoreactive patients

Ekaterina Kobal, M. Saidova, N. Danilov, O. Arkhipova, T. Martynyuk, I. Chazova. *Cardiology, Russian Cardiology Research and Production Complex, Moscow, Russian Federation*

The purpose: To estimate dynamics of right and left ventricular systolic and diastolic function by estimation Sa, Ea of the lateral tricuspid and mitral valve annulus during acute pharmacological testing (APhT) with inhaled nitric oxide (iNO) in patients with idiopathic pulmonary arterial hypertension (IPAH).

Materials and methods: In the study we included 11 pts (11 females) with IPAH aged 31-51 (mean age 39,8±7,4 years). All pts were performed right heart catheterization (RHC) with APhT and noninvasive vasodilator testing with iNO (20ppm for 10 min) before two hours to RHC. The estimation of SPAP was performed initially at rest and then at 10 min of nitric oxide Inhalation. All pts were responders. Echo included routing parameters and TVI was used for the estimation of systolic and diastolic function of RV/LV before and after APhT.

Results: In pts with IPAH (functional class II-III, WHO) the mean value of tricuspid regurgitation (TR) gradient was 64,8±11,5mmHg. In all pts included in the study the degree of TR was at least III. Taking into account right atrial pressure levels mean SPAP was 75±11,6mmHg by Transthoracic Doppler Echocardiography (TDEcho.) before APhT. Mean SPAP was 47,5±6,2mmHg. by echo after APhT. According to RHC data mean SPAP was 76,8±16,6mmHg. before test and 46,6±7,9mmHg after iNO. We found no significant dynamic of routine echo parameters. To 10' of iNO there was significant improvement Sa, Ea of RV during APhT with iNO. There was improvement Sa, Ea of LV but not significant.

Conclusion: TDEcho. may be used for an accurate assessment of vasodilator response as compared to RHC data. During APht with iNO only Sa, Ea of RV may be used for detecting vasoreactive patients.

P3917

Subtle assessment of quality of life in PH patients on inhaled iloprost treatment

Vera Reuber, Henning Tiede, Frank Reichenberger, Robert Voswinckel, Friedrich Grimminger, Werner Seeger, Ardeschir Ghofrani. *University of Giessen Lung Center, University Hospital, Giessen, Germany*

Background: Pulmonary hypertension (PH) is a disease characterized by vasoconstriction, remodeling of the small pulmonary vessels, and a lack of endogenous prostacyclin. Prostacyclin and its analogues are potent vasodilators and widely used in PH treatment. Information on the quality of life of PH patients is limited.
Methods: 74 patients who suffer from different forms of PH and receive inhaled Iloprost, either as first line or as add-on therapy, are followed. Patients received questionnaires concerning multiple aspects of their quality of life. NYHA functional class (NYHA), 6-minute-walk-distance (6MWD), results of the right-heart catheterization, and biomarker levels were recorded at the moment of baseline and follow-up (Nov. 2007 - Feb. 2009).
Results: 76% of patients described an improved state of health compared with the situation before start of inhalation. Furthermore significant correlations between quality of life and other important measures of PH could be shown. Improvements of NYHA-class, 6MWD, laboratory values (uric acid, BNP) and also of hemodynamic measurements (i.e. mPAP, PVR, CO, CI) during inhalative therapy with iloprost were detected. 6MWD improved significantly from 314.2±128.8 m to 354.4±131.0 m ($p<0.001$). 11 patients (23%) could improve their NYHA-class, 32 (66.6%) stayed unchanged and 5 (10.4%) deteriorated. These differences between baseline and follow up are significant ($p<0.001$).
Conclusion: Quality of life is an important measure for PH patients. Improvement in quality of life correlated very well with other important measures of PH.

P3918

The clinical relevance of heart rate increase in the interpretation of six-minute walk test in pulmonary hypertension

Gabor Kovacs[1,2], Christina Stöckl[1], Alexander Avian[3], Xhylsime Kqiku[1], Vasile Foris[2], Maria Tscherner[1,2], Horst Olschewski[1,2]. *[1]Pulmonology, Medical University of Graz, Austria; [2]PL-D, Ludwig Boltzmann Institute for Lung Vascular Research, Graz, Austria; [3]Medical Informatics, Statistics and Documentation, Medical University of Graz, Austria*

Background: Six-minute walk test (6MWT) is an important prognostic marker in pulmonary hypertension (PH). We hypothesized that clinical improvement might not only be characterized by an increased walk distance but also by changes in Borg dyspnea score (BDS) and heart rate.
Patients and methods: Patients with PH and subjects without PH but with abnormal exercise-induced pulmonary arterial pressure (PAP) increase were included. Each patient performed a 6MWT with "normal", "less than normal" and "more than normal" effort.
Results: 23 patients with PH (n=11pulmonary arterial hypertension, n=10 chronic thromboembolic PH, n=2 other; mean PAP: 40±12mmHg) and 6 subjects with abnormal exercise-induced PAP increase (resting mean PAP: 16±4mmHg) participated. 6MWT were 482±98, 447±80 and 402±82m in the walks with "more than normal", "normal" and "less than normal" effort (472±104 vs 437±84 vs 392±84m in PH patients). The respective BDS and heart rate increase was 3.2±1.5, 2.0±1.2 and 0.7±0.9, and 38±16, 31±14 and 23±14 min^{-1} (3.0±1.4, 2.0±1.3 and 0.8±0.9, and 40±16 vs 34±13 vs 23±15 min^{-1} in PH patients). The difference in walk distance between "less than normal" and "more than normal" tests was associated with the difference in heart rate increase during the test ($p=0.001$, $r=0.61$ in all subjects; $p<0.001$, $r=0.76$ in PH patients). On average, an 80m increase in 6MWT was associated with an additional 15 min^{-1} heart rate increase. Between the BDS and 6MWT there was no significant correlation.
Conclusion: Based on our pilot study, heart rate may be suitable to assess the effort level of subjects and may be incorporated to refine 6MWT in the follow-up of PH patients.

P3919

Wrist actigraphy predicts outcome in patients with pulmonary hypertension

Silvia Ulrich[1], Manuel Fischler[2], Rudolf Speich[3], Konrad E. Bloch[4]. *[1]Heart-Vessel-Thorax, Respiratory Clinic, University Hospital, Zurich, Switzerland; [2]Internal Medicine, City Hospital Waid, Zurich, Switzerland*

Rationale: Pulmonary hypertension (PH) impairs quality of life, exercise and survival. Simple measures to monitor the disease are needed. We tested whether actigraphy by a wrist-worn device in the patients home reflects disease severity in PH patients.
Methods: We studied 23 outpatients with precapillary PH (15 females) in WHO functional classes II-IV. Evaluations comprised clinical examination and actigraphy during 2 weeks while patients pursued their usual life at home. Actigraphies were correlated with clinical data and mean pulmonary artery pressure (mPAP). Deaths, lung transplantations and pulmonary endarterectomy were recorded during 4 years.
Results: Actigraphies revealed a mean±SD day-time with activity of 14:57±1:14 hours, activity counts were 146±125/min. Very severely impaired patients (mPAP 50±7 mmHg) rested more time immobile during nights (8:25±1:18h) and were less active during days (54±44 counts/min) compared to modestly impaired patients (mPAP 33±7 mmHg; night-time immobile 6:58±0:39h; day-time activity 229±148 counts/min, $P<0.05$ all instances). Of 19 patients followed for 4 years, 5 died, 1 underwent lung transplantation. Kaplan-Meier analysis revealed a shorter survival without lung transplantation in patients being active for less than 15h per day compared to patients with more than 15h of activity per day (log-rank $P=0.026$).
Conclusion: A long nocturnal rest and reduced day-time activity recorded by actigraphy are associated with severe hemodynamic impairment and reduced survival in patients with PH. Therefore, wrist actigraphy performed during everyday life in the patient's home holds promise as a simple tool for assessment of disease severity and prognosis in patients with PH.

P3920

Central venous-to-arterial carbon dioxide difference (CO2 GAP) in patients with arterial pulmonary hypertension: A pilot study

Marcelo Rocha, Fabrício Costa, José Erirtônio Façanha Barreto. *Pulmonology, Hospital de Messejana, Fortaleza, CE, Brazil Pulmonology, Hospital de Messejana, Fortaleza, CE, Brazil Interventionist Cardiology, Hospital de Messejana, Fortaleza, CE, Brazil*

Pulmonary arterial hypertension (PAH) is characterized by increased pulmonary vascular resistance that can lead to right failure and death. Right ventricular (RV) function is a major determinant of functional capacity and prognosis in PAH, with a reduced survival in patients with decreased cardiac index. Several studies have already shown that venous-to-arterial CO2 difference (CO2 GAP: PvCO2 minus PaCO2) is inversely correlated to cardiac index (CI) in septic and non-septic circulatory failure.
Objectives: To analyze the value of the CO2 GAP in PAH patients and its relationship with the cardiac index.
Methods: The right heart catheterization was performed using the Seldinger technique with a 8F sheath inserted via the basilica vein. Cardiac output was measured using thermodilution technique.
Results: We analyzed 26 patients with PAH (80% women and 20% men). 86% were classified as WHO group 1(34% had idiopathic PAH) and 7% were WHO group 4 (chronic thromboembolic pulmonary hypertension). Most patients were in NYHA functional class II (50%) and the mean 6-min walk distance was 451 meters. At the time of enrollment, 78% were treated with pulmonary vasodilators (39% sildenafil alone and 39% sildenafil + bosentana). CI, CO2 GAP and central venous oxygen saturation (ScvO2) were compared by Pearson correlation. We found a negative correlation between CI and CO2 GAP (R square 0,15 and p: 0,04) and a positive correlation between CI and venous O2 saturation (R square 0,44 and p: 0,0002).
Conclusion: In PAH patients, the CO2 GAP may be a useful tool to analyze right ventricular function. Future research should analyze its value in the prognosis of PAH patients.

P3921

Psychometric validation of the living with pulmonary hypertension questionnaire in pulmonary arterial hypertension patients

Nicola Bonner[1], Linda Abetz[1], Juliette Meunier[2], Mirko Sikirica[3]. *[1]PRO, Adelphi Values, Bollington, Cheshire, United Kingdom; [2]Statistics, Mapi Consultancy, Lyon, France; [3]GHEOR General Medicine, Bayer Healthcare, Berlin, Germany*

Background: The Living with Pulmonary Hypertension questionnaire (LPH) was adapted from the Minnesota Living with Heart Failure Questionnaire for use in patients with pulmonary arterial hypertension (PAH).
Objectives: To confirm the structure, assess the psychometric properties and provide guidance for the interpretation of the LPH.
Methods: LPH was given at baseline and last visit (week 12) to patients with PAH as part of a double blind, Phase III, clinical trial; this data was used to perform the LPH validation analyses: description of items, scores and quality of completion, construct validity, reliability, clinical validity and responsiveness. Analyses to provide an estimation of the Minimal Important Difference (MID) for the LPH scores were performed.
Results: The LPH Emotional and Physical scores met the criteria for convergent and discriminant validity; for the total score all but two items met the test for item convergent validity. Internal consistency reliability of the LPH scores was demonstrated by Cronbach's alpha values of >0.70 for all LPH scores. The LPH Physical and Total scores discriminated between World Health Organisation (WHO) Functional classes and 6 Minute walking test scores, indicating clinical validity and were also responsive to change in clinical severity, as measured by change in WHO functional class and Borg CR 10 Scale. Further investigation is required to confirm the responsiveness of the Emotional score. Estimation of MID using distribution-based methods indicated a change of 3 points for the sub-scales and 7 for the total score to be clinically meaningful.
Conclusion: The LPH is a valid and reliable instrument.

P3922

Modern age pathology of pulmonary arterial hypertension

Elvira Stacher[1,2,3], Brian Graham[3], James Hunt[3], Aneta Gandjeva[3], Steve Groshong[4], Vallerie McLaughlin[5], Marsha Jessup[5], William Grizzle[6], Carlyne Cool[3], Rubin Tuder[3]. *[1]Institute of Pathology, Medical University of Graz, Austria; [2]Ludwig Boltzmann Institute for Lung Vascular Research, Ludwig Boltzmann Society, Graz, Austria; [3]Program in Translational Lung Research, Division of Pulmonary Sciences and Critical Care Medicine, Anschutz Medical Campus, Aurora, CO, United States; [4]Department of Pathology, National Jewish Hospital, Denver, CO, United States; [5]Cardiovascular Center, University of Michigan Health System, Ann Arbor, MI, United States; [6]Department of Pathology, University of Alabama, Birmingham, AL, United States*

Introduction: The impact of modern treatments of pulmonary arterial hypertension (PAH) on pulmonary vascular pathology remains unknown. The last series reporting the pathology of severe pulmonary hypertension date back two decades, well before usage of current therapies for the disease.
Methods: Assessment of pulmonary vascular remodelling and inflammation in 62 PAH and 28 control explanted lungs systematically sampled, with matched clinical data. The tissue was obtained by the Pulmonary Hypertension Breakthrough Initiative.
Results: Total wall, intima, and media fractional thicknesses of pulmonary arteries were increased in the PAH group versus the controls, and correlated with pulmonary hemodynamics. Despite a high variability of morphological measurements within a given PAH lung and among all PAH lungs, pathological subphenotypes were detected in cohorts of PAH lungs. This included a subset of lungs lacking intima or media remodeling, which had similar numbers of profiles of plexiform lesions as those in lungs with more pronounced remodeling. Perivascular inflammation was present in a high number of PAH lungs and correlated with mean pulmonary arterial pressure (mPAP) as well as intima and total wall thickness. The number of profiles of plexiform lesions was significantly lower in lungs of patients who were never treated with prostacyclin or its analogues.
Conclusions: Our results indicate that multiple features of pulmonary vascular remodeling are present in patients treated with modern PAH regimens. Perivascular inflammation may have an important role in the processes of vascular remodeling, all of which may ultimately lead to increased pulmonary artery pressure.

P3923

The proANP increase during exercise may predict the PAP increase in connective tissue disease patients at risk of PAH

Maria Tscherner[1,2], Gabor Kovacs[1,2], Friedrich Fruhwald[3], Robert Maier[3], Barbara Obermayer-Pietsch[4], Alexander Avian[5], Vasile Foris[2], Horst Olschewski[1]. *[1]Internal Medicine, Division of Pulmonology, Medical University of Graz, Austria; [2]PLD, Ludwig-Boltzmann-Institute for Lung Vascular Research, Graz, Austria; [3]Internal Medicine, Division of Cardiology, Medical University of Graz, Austria; [4]Internal Medicine, Division of Endocrinology and Metabolism, Medical University of Graz, Austria; [5]Institute for Medical Statistics, Medical University of Graz, Austria*

Background: Natriuretic peptides (brain natriuretic peptide (BNP) and atrial natriuretic peptide (ANP)) are produced in cardiomyocytes of different myocardial regions. In case of dilation of the heart, BNP and ANP are excessivly released into the circulation. BNP is used as a biomarker in patients with chronic heart failure and pulmonary hypertension (PH). ANP is a marker of acute cardiac stress and may reflect actual hemodynamic changes during exercise. In connective tissue disease (CTD) an excessive increase of pulmonary pressure may represent an early stage of pulmonary vascular disease and may be clinically relevant.
Patients and methods: We investigated plasma levels of proANP and NTproBNP during right heart catheterization at rest and exercise in patients with CTD without PH. The levels at rest and during exercise were compared by Wilcoxon signed rank test. The correlations between the changes of meanPAP and NTproBNP as well as meanPAP and proANP were calculated by Spearman's test.
Results: N=47 patients (resting meanPAP: 16±3 mmHg, meanPAP at maximal exercise: 37±8 mmHg) were included. NTproBNP and proANP significantly increased from rest to exercise (NTproBNP rest: 91±102 pg/mL, max. exercise: 96±96 pg/mL, $p<0.001$; proANP rest: 2.43±1.22 pg/mL, maximal exercise: 2.92±1.33 pg/mL, $p<0.001$). The increase in proANP levels between rest and maximal exercise significantly correlated with the increase in meanPAP ($p= 0.007$, $r= 0.404$), but there was no significant correlation for NTproBNP ($p=0.606$).
Conclusion: Our results suggest that the exercise induced increase of proANP in patients with connective tissue disease may indicate the exercise-induced increase in PAP.

P3924

Prognostic value of pulmonary function testing in idiopathic pulmonary hypertension – The most relevant differences between survivors and non-survivors in three-years observation study

Monika Szturmowicz[1], Aneta Kacprzak[1], Monika Franczuk[2], Agnieszka Skoczylas[3], Anna Fijalkowska[4], Marcin Kurzyna[5], Stefan Wesolowski[2], Adam Torbicki[5]. *[1]Dept. of Lung Diseases, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland; [2]Dept. of Pathophysiology, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland; [3]Outpatients Department, Pulawska Medical Center, Warsaw, Poland; [4]Dept. of Radiology, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland; [5]Dept. of Cardiology, European Health Center, Warsaw, Otwock, Poland*

Introduction: The risk stratification in idiopathic pulmonary hypertension (IPAH) is currently based on hemodynamic and functional parameters. Clinical significance of pulmonary function testing (PFT) is not well defined.
Aim: The aim of the study was to analyze the prognostic value of PFT in IPAH patients (pts) during three-years observation period.
Material: 65 IPAH pts, mean age 41.5 (±14.5) years, mean (m)PAP – 57.3 (±12.5) mmHg, mRAP – 8.9 (±5.2) mmHg, mCI – 2.5 (±0.7) L/min/m^2, msatO2mv - 56.8 (±9.1)%. PFT was performed in all of the patients according to ERS guidelines. Survival time was assessed from PFT till the death, lung transplantation or the end of observation time. The prognostic value of selected variables was tested by Cox proportional hazards regression analysis.
Results: The following differences in median PFT values between survivors (50 pts) and non-survivors (15 pts) were noted: FEV1 (%pred.) – 100.2 vs 85.8 ($p=0.01$), FEV1/VC – 0.77 vs 0.74 ($p=0.03$), VC (%pred.) 109.2 vs 103.1 (ns), MMEF (%pred.) – 75.8 vs 46.4 ($p=0.02$), DLCO (%pred.) – 74.2 vs 52.0 ($p=0.005$), TLC-VA (ml) – 660 vs 1170 ($p=0.005$). DLCO (%pred) (HR: 0.97, $p=0.005$) and TLC-VA (HR: 2.15, $p=0.03$) were significant prognostic variables in univariate analysis. DLCO<60%pred, pO2<60 mmHg and satO2mv< 63% were significant prognostic indicators in multivariate analysis.
Conclusions: Three- years survivors comparing to non-survivors had significantly higher DLCO% pred. and less disturbances of gas distribution expressed as TLC-VA. Nevertheless only DLCO %pred. was an independent prognostic variable.

P3925

Acquisition of echo-Doppler parameters of pulmonary hypertension in COPD

Andrew Goudie, Pippa Hopkinson, William Anderson, Brian Lipworth, Allan Struthers. *Centre for Cardiovascular and Lung Biology Research, University of Dundee, United Kingdom*

Background: Pulmonary hypertension in COPD is of key prognostic significance. Doppler echo in the presence of TR can estimate RVSP/sPAP. Acquisition rates and TR jet quality are reduced in COPD due to hyperinflation. TR jet quality influences pressure estimation accuracy. An alternative assessment for PH is the time to peak pulmonary flow velocity, pulmonary acceleration time(ACT). An ACT <105 ms suggests PH. We examined the availability/quality of TR jet vs. pulmonary flow waves (PFW) in COPD.
Methods: COPD patients were invited for echo and PFTs. Availability/quality of TR jet and PFWs were assessed. RVSP was calculated from the max. TR velocity. RAP=10 mmHg. ACT was a 3 measurement avg. using pulse wave Doppler placed in the right ventricular outflow tract.
Results: A total of 63 patients were screened, 63% male. Mean age 67.8 years(SD8.3); FEV_1 1.2 L(0.5);FEV_1% 47.3%(16.7);RV/TLC 55%(8.8);SaO_2 95.0%(3.6). TR was detected in 43 patients(68%) where TR jet was sufficient for RVSP measurement in 28(44% of total cohort). TR jet quality was poor, fair, good and excellent in 17,10,12, and 4 subjects respectively. Mean RVSP 43 mmHg, 95% CI[39-47]. ACT was measurable in 61 patients(97%) with good or excellent quality PFWs in 58 (95%). Mean ACT 113 ms, 95% CI[108-118]; mean mPAP 25 mmHg, 95% CI[23-28]. Subcostal vs. parasternal acquisition of ACT resulted in superior availability and quality in 80% of patients.
Conclusion: Contrasting RVSP, ACT is available in almost all COPD patients. TR jet quality is commonly poor whereas that of PFWs is frequently excellent due to the ease of subcostal acquisition. These findings suggest that in addition to RVSP, ACT should be measured routinely when assessing COPD patients for PH.

P3926

Telemetric right ventricular pressure measurements and serial echocardiography in experimental pulmonary arterial hypertension

Michiel Alexander de Raaf, Ingrid Schalij, Anton Vonk-Noordegraaf, Frances de Man, Harm Jan Bogaard. *Department of Pulmonary Medicine, VU University Medical Center, Amsterdam, Netherlands*

This study characterized hemodynamic changes in the Sugen-Hypoxia (SuHx) model by telemetric acquisition and echocardiography. The SuHx rat model is based on the combined exposure to the VEGF-receptor inhibitor SU5416 and hypoxia and is used in Pulmonary Arterial Hypertension (PAH) research due its histological features resembling the plexogenic pulmonary vascular remodeling seen in human PAH.
SU5416 (25 mg/kg s.c.) was administered and animals were housed at 10% oxygen for 4 weeks, followed by re-exposure to normoxic conditions. Telemetric right ventricular pressure acquisition was continuous from surgery onwards. Serial echocardiography was performed weekly under anesthetic conditions. Spearman correlations were calculated between echocardiographic parameters and telemetric RVSP.
Telemetric RVSP increased immediately after administration of SU5416 and exposure to hypoxia. In the consecutive re-exposure to normoxic conditions, a considerable interindividual variability was observed. Echocardiographic parameters as Tricuspid Annular Plane Systolic Excursion (TAPSE), Right Ventricular End Diastolic Diameter (RVEDD) and Pulmonary Artery Acceleration Time divided by cardiac cycle length (PAAT/cl) showed hypoxic adaptation, but post-hypoxic

differences were less pronounced. RVEDD, but not PAAT/cl and TAPSE was significantly correlated to RVSP.
Telemetry and echocardiography both show a progressive response in the hypoxic period. Individual variability among animals resulted in different RVSP-responses upon re-exposure to normoxic conditions. RVEDD correlated significantly with RVSP, whereas TAPSE and PAAT/cl seemed not suitable as surrogate markers for RVSP.

P3927
Correlation of computed tomography measurement of small puomonary vessels with hemodynamic factors in pulmonary arterial hypertension
Yukiko Matsuura, Toshihiko Sugiura, Naoko Kawata, Nobuhiro Tanabe, Koichiro Tatsumi. *Respirology, Graduation School of Mrdicine, Chiba University, Chiba, Japan*

Background: Previous studies have shown that the percentage of total cross-sectional area of small pulmonary vessels (CSA) for the lung area assessed on computed tomography (CT) is significantly correlated to pulmonary arterial pressure in patients with severe emphysema.
Purpose: We aimed to study correlation of the percentage of CSA less than 5mm^2 (%CSA<5) with hemodynamic factors in patients with pulmonary arterial hypertension (PAH).
Materials and methods: 14 subjects (5 male, 53±12 yrs) with PAH underwent noncontrast CT scan and right heart catheterization (RHC). Three CT slices were selected from noncontrast CT images. The upper cranial slice was taken approximately 1 cm above the upper margin of the aortic arch, the middle slice was taken approximately 1 cm below the carina, and the lower caudal slice was taken approximately 1 cm below the right inferior pulmonary vein. We measured CSA less than 5mm^2 and lung area from each images, and calculated the percentage of total CSA for the lung area(%CSA<5). The correlation of %CSA<5 and hemodynamic data obtained by RHC were evaluated.
Results: %CSA<5 was 1.12±0.26%. mean pulmonary arterial pressure(mPAP), systolic pulmonary arterial pressure (sPAP) and pulmonary vascular resistance (PVR) were 41±15 mmHg, 65±27 mmHg and 536±332 dyne sec cm^{-5}, respectively. The correlation coefficient of %CSA <5mm^2 with sPAP, mPAP and PVR were -0.60 (P=0.02), -59 (P=0.03) and -0.60 (P=0.02), respectively.
Conclusions: %CSA<5 measured on CT images significantly correlate with sPAP, mPSAP and PVR in subject with PAH.

P3928
Does lung function predict response to therapy in PAH associated with connective tissue disease?
Christopher Valerio[1], Benjamin Schreiber[1], Clive Handler[1], Christopher Denton[2], John Coghlan[1]. *[1]Pulmonary Hypertension, Royal Free Hospital, London, United Kingdom; [2]Rheumatology, Royal Free Hospital & UCL Medical School, London, United Kingdom*

Introduction: PAH specific therapies have been trialled in several lung diseases without success. It has also been shown that a low FVC is associated with a poor prognosis in CTD-PAH.
Methods: From the Royal Free Hospital pulmonary hypertension associated with connective tissue disease database we identified patients with lung function tests within 6 months of right heart catheterisation performed to confirm pulmonary hypertenson. Patients who had repeat haemodynamic studies within a year of diagnosis on first line therapy (bosentan) were included.
Results: There were no significant haemodynamic differences between groups at baseline (ANOVA). Follow up catheter studies demonstrated a good haemodynamic response with improvements in mean PA pressure (FVC >94%) and pulmonary vascular resistance (FVC >70%).

	FVC <70, n=23	FVC 70-94, n=28	FVC >94, n=30
Baseline RAP mmHg	8.3	7.8	6.6
Baseline mPAP mmHg	39.3	44.3	39.8
Baseline PCWP mmHg	10.2	9.9	9.8
Baseline PVR dynes·cm/5	553	670	565
Baseline CI L/min/m^2	2.6	2.6	2.7
F/u RAP	7.9	8.2	6.5
F/u mPAP	37.4	43.0	36.4*
F/u PCWP	9.3	10.5	10.3
F/u PVR	496	590*	476*
F/u CI	2.6	2.7	2.8
One year survival	91%	93%	100%

RAP = right atrial pressure, mPAP = mean pulmonary artery pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular resistance, CI = cardiac index. *p<0.05 compared with baseline paired Students' t-test.

The changes seen in the FVC <70% group did not reach significance (e.g. p<0.09 for PVR).
Conclusion: A low FVC does not preclude a good treatment response, suggesting that PAH can co-exist with lung fibrosis in connective tissue diseases. Treatment of both pathologies may be needed to improve outcomes in this difficult group.

P3929
Change in diffusing capacity for carbon monoxide as a predictor of outcomes in connective tissue disease-associated pulmonary arterial hypertension: Analysis from the REVEAL registry
Roham Zamanian[1], Kristina Kudelko[1], Dave Miller[2], Michael McGoon[3], Raymond Benza[4], Paul Hassoun[5], Mark Nicolls[1], Lorinda Chung[6]. *[1]Division of Pulmonary & Critical Care Medicine, Stanford University School of Medicine, Stanford, CA, United States; [2]Statistical Analysis, ICON Late Phase & Outcomes Research, San Francisco, CA, United States; [3]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, United States; [4]Division of Cardiology, Allegheny General Hospital, Pittsburgh, PA, United States; [5]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, United States; [6]Immunology & Rheumatology, Stanford University Medical Center, Palo Alto, CA, United States*

Background: Change in diffusing capacity for carbon monoxide (DLCO) is a more powerful predictor of outcomes than baseline DLCO in connective tissue disease (CTD)-associated pulmonary arterial hypertension (PAH).
Aims and objectives: We sought to validate these findings in a larger, multi-center CTD-APAH cohort.
Methods: CTD-APAH patients (pts) in the Registry to EValuate Early And Long Term PAH Management (REVEAL), comprising 3515 pts with PAH from 56 US centers, were divided into 3 cohorts based on change in DLCO over time: 1) decreased by >10% ($DLCO_{dec}$), 2) unchanged within ±10% ($DLCO_{stab}$), 3) increased by >10% ($DLCO_{inc}$). Two-year survival after second DLCO assessment was evaluated.
Results: 249 CTD-APAH pts were analyzed. Most pts were women (87.9%), with Ssc-APAH (73.9%), functional class II & III symptoms (77.9%), and on PAH therapies (83.9%). While 66.3% of pts were stable over time, 25.3% had reduced (-20.1±12.4%) and 8.4% improved (25.1±18.2%) DLCO. Mean time between DLCO measurements did not differ between $DLCO_{dec}$ and $DLCO_{inc}$ pts (34.6±28.6 vs. 29.7±25.2 mos., P>0.05). All deaths (80) occurred in $DLCO_{dec}$ and $DLCO_{stab}$ cohorts. The $DLCO_{inc}$ cohort had the best 24-month survival (log-rank p=0.007, $DLCO_{inc}$ vs. $DLCO_{stab}$). Multivariable analysis showed $DLCO_{dec}$ as a predictor of worst survival (HR 2.8, CI=1.65-4.73, P<0.001).
Conclusion: Increase in DLCO by >10% was associated with improved outcomes in CTD-APAH. Identification of mechanisms and role of therapies in DLCO enhancement needs further investigation and may provide significant insights into future clinical care of patients with PAH.

P3930
Histopathology of idiopathic pulmonary arterial hypertension in patients with low or normal diffusion capacity
Esther Nossent[1], Pia Trip[1], Harm jan Bogaard[1], Anco Boonstra[1], Anton Vonk-Noordegraaf[1], Katrien Grunberg[2]. *[1]Pulmonary Diseases, VU University Medical Center, Amsterdam, Netherlands; [2]Pathology, VU University Medical Center, Amsterdam, Netherlands*

Introduction: In patients with Idiopathic Pulmonary Arterial Hypertension (IPAH) a wide range of diffusion capacity for carbon monoxide (DLCO) values can be observed. Low DLCO in IPAH is associated with worse prognosis when compared to normal DLCO[1].
Hypothesis: Histopathological pattern(s) of pulmonary vasculopathy in IPAH differ between patients with low and normal DLCO.
Methods: We retrospectively analyzed the histopathological (combinations of) patterns of vasculopathy in IPAH patients with low and normal DLCO. Low DLCO was defined as lowest tertile of the bimodal distribution of DLCO-value in a series of 170 IPAH patients[1] (<45% pred.). DLCO in the upper 2 tertiles (≥45% pred.) was defined as normal DLCO.
Results: Out of 170 IPAH patients, complete data sets were obtained in 20 patients: low DLCO N=10; normal DLCO N=10. Results are shown in table 1 (study is ongoing).

Table 1. Histopathology

	Low DLCO (N=10)	Normal DLCO (N=10)
Lung biopsies	3	7
Explant	2	–
Autopsy	5	3
Pulmonary vasculopathy pattern		
Plexogenic arteriopathy	–	5
Thrombotic arteriopathy	1	2
Hypoxic arteriopathy	1	2
PVOD*/PCH** pattern	6	1
Congestive vasculopathy	2	1
No specific pattern	1	2

*Pulmonary Veno-Occlusive Disease, **Pulmonary Capillary Haemangiomatosis.

Conclusion: A PVOD/PCH-like pattern is more common in IPAH with low DLCO, while plexogenic arteriopathy prevails in IPAH with normal DLCO.
Reference:
[1] Trip *et al,* abstract this meeting.

P3931

Prognostic relevance of changes in exercise parameters in pulmonary arterial hypertension

Herman Groepenhoff, Anton Vonk-Noordegraaf, Anco Boonstra, Nico Westerhof, Harm Jan Bogaard. *Institute for Cardiovascular Research and Department of Pulmonology, VU University Medical Center, Amsterdam, Netherlands*

Introduction: Exercise parameters measured at baseline predict survival in pulmonary arterial hypertension (PAH). However, it has not been determined whether changes in exercise parameters after follow up are useful to guide clinicians in their choices for (adjustment of) PAH treatment. The aim of this study was to determine changes in exercise variables after one year of PAH specific therapy and to relate these changes to subsequent survival.
Methods: One year changes in cardiopulmonary exercise test variables and six minute walking distance (6MWD) were related to survival using Univariate Cox regression and Kaplan-Meier analysis in 40 PAH patients (mean age 44±2 yrs).
Results: After a mean follow up time of 81 (± 5) months, two patients were scheduled for lung transplantation and 10 had died. Survival analysis showed that from all exercise variables only one-year changes in maximal oxygen uptake (VO_2), VO_2/heart rate (O_2pulse) and 6MWD were significant predictors of survival. Kaplan-Meier analysis (with ideal cut-off points estimated by receiver operating analysis) showed that patients with > 5% increase in VO_2 or O_2pulse had a significantly better cumulative survival (78±12% and 78±10%, respectively) compared to patients with < 5% increase in VO_2 or O_2pulse (cumulative survival 40±13% and 27±20%, respectively). Patients with < 6% decrease in 6MWD had a significantly better cumulative survival (84±7%) compared to patients with > 6% decrease in 6MWD (cumulative survival 25±15%).
Conclusion: Changes in VO_2, O_2pulse and 6MWD from baseline to one year of follow up predict survival in PAH. Consequently, these variables could be considered to guide treatment in PAH patients.

P3932

Iron deficiency in patients with systemic sclerosis-associated pulmonary arterial hypertension

Gerrina Ruiter[1,2], Alexandre Voskuyl[3], Irene Lanser[1], Frances de Man[1,2], Pieter Postmus[1], John Wharton[4], Nico Westerhof[2], Willem van der Laarse[2], Luke Howard[5], Martin Wilkins[4], Anton Vonk-Noordegraaf[1]. *[1]Pulmonology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, Netherlands; [2]Physiology, Institute for Cardiovascular Research, VU University Medical Center, Amsterdam, Netherlands; [3]Rheumatology, VU University Medical Center, Amsterdam, Netherlands; [4]Pharmacology and Therapeutics, Experimental Medicine, Hammersmith Hospital, Imperial College London, United Kingdom; [5]National Pulmonary Hypertension Service, Hammersmith Hospital, Imperial College London, United Kingdom*

Background: Systemic sclerosis-associated pulmonary arterial hypertension (SSc-PAH) has a poor clinical outcome compared to other types of PAH. Recent data has shown that iron deficiency (ID) is associated with poor survival in idiopathic PAH. Inflammatory cytokines and increased hepcidin levels play a role. We hypothesise that a high prevalence of ID in SSc-PAH is linked to poor clinical outcome.
Methods: Measures of body iron status were performed retrospectively in serum from SSc-PAH patients (n=49) and systemic sclerosis patients without PAH (SSc, n=131). Six minute walking distance (6MWD) was also compared between the groups.
Results: Circulating soluble transferrin receptor (sTfR) levels in SSc-PAH patients were higher than in SSc ($p<0.001$) while circulating iron, ferritin and transferrin saturation were reduced. The prevalence of ID, defined by sTfR >28.1 nmol/L, was 47% in SSc-PAH compared to 20% in SSc ($p<0.001$). Although hepcidin levels were lower in SSc-PAH than in SSc patients ($p<0.001$), hepcidin in both groups were high compared to reference values. There was no significant correlation with interleukin-6 (IL-6) levels ($p=0.82$), since IL-6 was higher in SSc-PAH compared to SSc patients ($p<0.01$). 6MWD was lower in SSc-PAH compared to SSc patients ($p<0.001$) and was even more reduced in case of ID (SSc-PAH with ID vs SSc-PAH without ID, $p<0.05$).
Conclusions: Iron deficiency is more prevalent in SSc-PAH than in SSc patients and is associated with lower exercise capacity. The role of hepcidin in this process remains to be elucidated.

P3933

The sPAP/VO2 ratio during cardiopulmonary exercise testing as predictor of manifest pulmonary hypertension

Frank Reichenberger[1,3], Robert Voswinckel[1], Melanie Thamm[1], Friedrike Lendeckel[1], Richard Schulz[1], Malte Kappert[1], Julia Dämming[1], Rory Morty[1], Christian Tanislav[2], Hossein Ardeschir Ghofrani[1], Werner Seeger[1], Henning Tiede[1]. *[1]University Giessen Lung Center, University Hospital, Giessen, Germany; [2]Department of Neurology, University Hospital, Giessen, Germany; [3]Department of Pneumology, Asklepios Lung Hospital, München-Gauting, Germany*

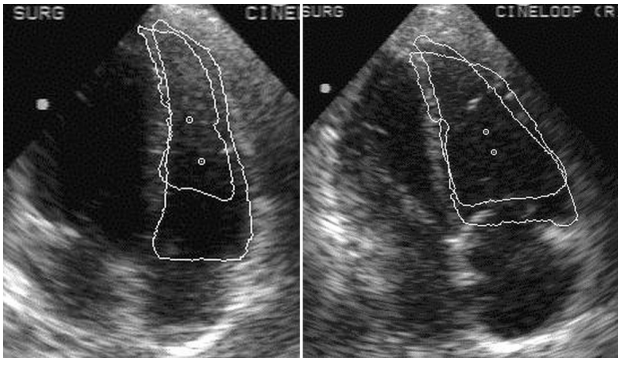
Background: Pulmonary hypertension (PH) is characterised by an inappropriate increase of pulmonary artery pressure (PAP) compared to cardiac output. We evaluated the systolic PAP (sPAP) during cardiopulmonary exercise test (CPET) in relation to maximum oxygen uptake (VO2max) as surrogate for cardiac output.
Patients and methods: We evaluated the sPAP/VO2max ratio in respect to presence or absence of PH. We retrospectively analysed right heart catheters studies (RHC) during CPET in 387 patients referred for workup of PH. We prospectively validated the ratio in 52 patients with normal echocardiography at rest, who underwent echocardiography during CPET followed by RHC.
Results: In the retrospective study, a manifest PH was found in 97 patients (69 precapillary PH, 28 postcapillary PH). The sPAP/VO2max ratio was mean 2,13 (SD 1,29) in both groups.
In 204 patients an exercise induced pulmonary hypertension (eiPH, mPAP > 30 mm Hg at maximum exercise) was diagnosed (96 precapillary eiPH, 108 postcapillary eiPH). The sPAP/VO2 max ratio was 1,25 (0,80) in both groups. In 86 patients with normal pulmonary circulation at rest and during exercise the sPAP/VO2max ratio was 0,97 (0,67).
ANOVA revealed highly significant differences of sPAP/VO2max ratio between the groups. The ROC analysis revealed a cut-off value of 0,61 with a sensitivity of 0,94 and specificity of 0,28 to detect manifest PH.
Prospectively, in 52 patients a sPAP/VO2max ratio < 0,61 at echocardiography during CPET could exclude manifest PH with a sensitivity of 100%.
Conclusion: A sPAP/VO2max can be measured by echocardiography during CPET. A ratio < 0.61 excludes manifest PH with a negative predictive value of 100%.

P3934

Novel method for assessment of the right ventricular contractile dysfunction in patients with severe COPD

Olena Krakhmalova, Daria Kalashnyk. *Cardiopulmonology, Institute of Therapy named after L.T.Maloy NAMS of Ukraine, Kharkiv, Ukraine Cardiopulmonology, Institute of Therapy named after L.T.Maloy NAMS of Ukraine, Kharkiv, Ukraine*

Aims and objectives: To develop a new diagnostic criterion for RV contractile function assessment in patients with COPD.
Methods: Forty patients with COPD of III-IV stages (mean age of 58,4±7,3) with precapillary pulmonary hypertension (PH, PA systolic pressure ± 43,9 mmHg) and 30 healthy individuals (mean age of 52,5±6,9) were examined. For each patient the calculation of the geometric center of the right ventricle (RVGC), amplitude and angle of RVGC vector displacement, using an original method for secondary processing of ultrasound images normal and for COPD.
Results: The amplitude of the RVGC movement in healthy individuals was a=1,8±0,36 cm vs a^1=0,92±0,23 cm in patients with COPD ($p<0,01$), and the angle of RVGC vector displacement in normal a=137±15° vs a^1=155±14° in COPD ($p<0,01$).



Conclusions: The assessment of amplitude and angle of movement of the RVGC vector can be used as a quantitative ultrasound criteria of the RV contractile dysfunction in COPD associated with PH.

P3935

Plasma high fibrinogen and low plasminogen levels predict poor prognosis in patients with inoperable chronic thromboembolic pulmonary hypertension

Fumiaki Kato, Nobuhiro Tanabe, Hajime Kasai, Ayumi Sekine, Takao Takeuchi, Takashi Urushibara, Rintaro Nishimura, Rika Suda, Takayuki Jujo, Toshihiko Sugiura, Ayako Shigeta, Seiichiro Sakao, Yasunori Kasahara, Koichiro Tatsumi. *Respirology, Graduate School of Medicine, Chiba University, Chiba-shi, Japan*

Background: Chronic thromboembolic pulmonary hypertension (CTEPH) comprises organizing thrombotic obstructions in the pulmonary arteries, and progressive pulmonary hypertension. However, there are few reports about the abnormality of coagulation and fibrinolysis system in CTEPH.
Purpose: The aim of this study was to investigate correlation between coagulation and fibrinolysis system, and severity and prognosis in patients with CTEPH.
Methods and results: We studied 91 patients (18 male, 55±14 [SD] years, mean pulmonary arterial pressure 45±12 mmHg) diagnosed as having inoperable CTEPH at Chiba University Hospital between 1986 and 2011. We retrospectively investigated the relationship between plasma fibrinogen and plasminogen levels,

severity and prognosis. Eighteen patients who had both high fibrinogen level (≥291 mg/dl, median) and low plasminogen level (<100.5 ng/ml, median) showed significantly lower cardiac index (2.27±0.66 vs. 2.70±0.58 L/min/m^2, p=0.0079), higher pulmonary vascular resistance (PVR) (1030±602 vs. 746±340 dyne*sec*cm^{-5}, p=0.0090), and poor survival (5-year survival 35.4 vs. 88.6%, p<0.001) compared with other 73 patients. Multivariate analysis revealed that plasma fibrinogen, plasminogen, and PVR were independent predictors for survival.

Conclusion: Plasma high fibrinogen and low plasminogen levels are poor prognostic factors for patients with inoperable CTEPH.