104. Pulmonary circulation: clinical diagnosis, treatment, end-points and animal models

P955

PLA2 polymorphism of platelet glycoprotein IIb/IIIa but not Factor V Leiden and prothrombin G20210A polymorphisms is associated with venous thromboembolism and more recurrent events

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Introduction: Inherited thrombophilic gene polymorphisms have been linked to the pathogenesis of venous thromboembolism (VTE). As they are very limited data of these polymorphisms in Iranian population we aimed to investigate them in these patients.
Methods: 72 patients with VTE and 306 healthy control subjects were recruited to the study. Genotyping from EDTA taken venous blood for the factor V Leiden (FVL), prothrombin (FII) G20210A, methylene tetrahydrofolate reductase (MTHFR) C677T and PLA2 polymorphisms was under taken by PCR – RFLP.
Results: 57of investigated polymorphisms with the mean of 0.792 per individual and 151 with the mean of 0.494 were found in patients and control respectively ($p<0.001$). FVL and FII G20210A were found in 5.6% and 1.4% of the patients compared with 2.3% and 1% of the controls respectively (P=NS). PLA2 polymorphism of GPIIb/IIIa was seen in 27.8% and 10.1% in patients and controls respectively (OR=3.4, CI= 1.08-6.44, $P<0.001$). 21.5% of carrier VTE patients compared with 9.6% of carrier controls had coinheritance of more than one genetic risk factor (P=0.007) and more recurrent events were occurred in them. Patients with PLA2 polymorphism had more recurrent events than the other patients (P=0.02). Patients with more than one genetic risk factors and recurrent events were younger.
Discussion: Higher prevalence of PLA2 polymorphism of GPIIa/IIIb in VTE patients demonstrates the impact of this polymorphism in the pathogenesis of VTE in this population that need to manage these patiant differently.

P956

Tetrahydrobioptherin improves pulmonary vascular remodeling following mouse-intratraqueal bleomicin administration

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Background/Objective: Pulmonary hypertension in pulmonary fibrosis portends a poor prognosis. Recent evidence suggests that tetrahydrobiopterin (BH4), the cofactor of nitric oxide synthase, is involved in pulmonary hypertension. However the role of BH4 in pulmonary hypertension secondary to pulmonary fibrosis is unknown. The current study investigated the role of BH4 on pulmonary remodelling in an animal model of bleomycin-induced lung fibrosis.
Methods: C57Bl/6J mice were instilled intratracheally with a single dose of bleomycin at 3.75 U/kg at day 1. BH4 (20mg/kg) or vehicle (control) was administered orally once a day, from day 1 until the end of experiment (day 14). At the end of the treatment period, mice were sacrificed and plasma, lungs and heart were removed. Plasmatic BH4 concentration was measured by high performance liquid chromatography. The right ventricular (RV) wall of the heart was dissected free and weighed along with the left ventricle wall plus septum (LV + S), and the resulting weights were reported as RV/LV + S ratio to provide an index of right ventricular hypertrophy. TGF-β1 and ET-1 gene expression were measured by real time RT-PCR in lung homogenates as pulmonary vascular remodeling markers.
Results: Bleomycin reduced ~2.3-fold the BH4 plasmatic levels, augmented the RV/LV + S ratio to 0,075 mg/mg over control, and increased the ET-1 and TGF-β1 gene expression to ~2-fold and ~6-fold versus control respectively. Oral BH4 suppressed the bleomycin-induced right ventricular hypertrophy and reduced the ET-1 and TGF-β1 gene expression to control levels.
Conclusions: BH4 inhibits bleomycin-induced right ventricular hypertrophy in mice.

P957

Molecular analysis of genes BMPR2 and KCNA5 in Spanish patients with pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH; OMIM 178600) is a rare and progressive vascular disorder characterized by obstruction of precapillary pulmonary arteries. PAH results from extensive remodelling of the pulmonary vasculature caused by an increased musculation of small arteries and the fibrosis of the intima that leads to obliteration of small pulmonary arteries. Without treatment, progression of pulmonary hypertension leads to right ventricular failure and death in three years from diagnosis. Approximately 75% of patients with the familiar form of PAH have a mutation in the gene encoding bone morphogenetic protein receptor type II (BMPR2). However, some other candidate genes have been advocated, including potassium voltage-gated channel, shakerrelated subfamily, member 5 (KCNA5).
We included 30 PAH patients and 50 controls. The DNA extraction was performed with Qiagen FlexiGene DNA kit. BMPR2 and KCNA5 genes were amplified by PCR and sequenced.
A total of 20 BMPR2 nucleotide changes were identified in 22 of 30 patients with PAH. Only 3 changes were identify with the Polyphen software as pathogenic (p.C84F, p.Q92L and p.W298Stop). These mutations were found in 4 patients. For KCNA5 gene 10 nucleotide changes were detected in 11 patients. Three were classified as pathogenic (p.P169R, p.R184P and p.E208X) we have found these mutations in 4 patients. None of the pathogenic mutations identified here were detected in a panel of 100 chromosomes from control individuals.
In conclusion, mutations in genes BMPR2 and KCNA5 have been detected in the 28,5% of our pool of patients indicating that these genes are the most important genes implicated in the development of PAH.

P958

The German version of the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) – Four-stage translation and validation

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Background and objective: Individuals with precapillary pulmonary hypertension (PH) experience impaired quality of life (QoL). A disease-specific outcome measure, the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) is validated in English. We translated the instrument and validated it for German-speaking population.
Methods: A multi-step procedure including bilingual translation process, lay panel assessment, cognitive debriefing interviews, validation and evaluation was performed. It included 107 patients with precapillary PH (60 females; age 60+15 years) from centres in Austria, Germany and Switzerland
Results: The translation process was straightforward. The field-test interview participants found the questionnaires relevant, comprehensible and easy to complete. Psychometric analyses showed that the German adaptations were successful. High test-retest coefficients for the scales after controlling for change in respondent's QoL (FC: 0.92 to 0.96; EC: 0.85 to 0.99) indicated a high degree of reliability. The CAMPHOR scales had good internal consistency (Cronbach's alpha coefficients 0.90 to 0.92 and 0.88 to 0.92, respectively). Also the three CAMPHOR scales (symptoms, activity limitations and quality of life) had excellent test-retest reliability (r=0.90-0.91, $P<0.001$) and internal consistency (Cronbach's alpha >0.90). Predicted correlations with the NYHA class, the 6-minute walking distance and the Nottingham Health Profile provided evidence of an excellent construct and group validity of the CAMPHOR scales.
Conclusions: We have shown the CAMPHOR to be valid and reliable in the German population and recommend its use in clinical practice.

P959

Reference values for the 6-minute walk test in healthy children

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Background: The 6 minute walk test (6MWT) is a simple and reliable tool to assess exercise capacity in various diseases. The aim of this study was to establish reference values for the 6MWT in healthy children and adolescents in middle

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Europe and to investigate the impact of age, anthropometrics, heart rate, blood pressure and reported physical activity on the distance walked.
Methods: Age- and sex-stratified children and adolescents between 5-17 years had short questionnaire assessments about their health state and physical activities. Thereafter anthropometrics and vitals were measured, a 6MWT was performed according to guidelines and exercise vitals were reassessed.
Results: Age-adjusted 6MWT distance from 496 children (252 girls) was obtained. Age, height, weight and the exercise heart rate all predicted the distance walked according to different regression models: age was the best single predictor and mostly influenced walk distance in younger age, anthropometrics were more important in girls and adolescents. Exercise heart rate was an important distance predictor in addition to age and outreached anthropometrics in the majority of subgroups assessed.
Conclusion: Performing the 6MWT is feasible and practical in children and adolescents. The 6MWD depends mainly on age, however, exercise heart rate, height and weight significantly add information and should be taken into account mainly in adolescents. Reference equations allow to predict 6MWT distance and may help to better assess and compare outcomes in young patients with cardiovascular diseases.

P960
The adenosine A2B receptor antagonist GS-6201 reduces small artery muscularization and plasma endothelin-1 in a short term cigarette smoke exposure model
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Adenosine plays an important role in the development and progression of lung injury with increased levels of adenosine and expression of A2B receptors. The A2B antagonist GS-6201 has shown anti-inflammatory effects in an acute model of cigarette smoke- induced lung injury. We have previously shown that exposure to cigarette smoke induces small artery remodeling and increased pulmonary arterial pressures in the guinea pig. Because A2B adenosine receptors are highly expressed in the pulmonary vasculature, we hypothesized that the A2B antagonist GS-6201 may prevent this remodeling. We exposed groups of six guinea pigs to 5 cigarettes per day 5 days per week for 4 weeks; groups were given oral vehicle or GS-6201 in doses of 3, 10 and 30 mg/kg (QD) 2 hours prior to smoke exposure, and a group was exposed to room air. 24 hours after final exposure, the animals were anesthetized and pulmonary arterial pressure was measured directly. One lung lobe was lavaged, and inflammatory cell counts obtained, one lobe was inflated with agarose for morphometric analysis of muscularization of the small pulmonary arteries. Plasma was obtained for measurement of endothelin-1 (ET-1. We found that cigarette smoke induced a non-significant increase of the pulmonary arterial pressure, but a significant increase in small arterial muscularization that was reduced by GS-6201 in a dose-dependent manner. Plasma ET-1 was increased by smoke exposure, and significantly decreased in a dose-dependent manner by GS-6201 as well. Our data suggest that adenosine receptor A2B antagonists may prevent the development of COPD associated pulmonary hypertension.

P961
End-tidal CO2 pressure may facilitate differential diagnostics between PH patients with chronic heart or lung disease and CTEPH
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Background: End-tidal CO_2 pressure ($PETCO_2$) is a simple parameter, which may be assessed at rest or during exercise during cardiopulmonary exercise testing (CPET). $PETCO_2$ changes have been described in patients with cardiac failure and acute pulmonary embolism, as well as in pulmonary hypertension (PH), but it is not known if PETCO2 may be helpful in differentiating between PH subgroups.
Patients and methods: We retrospectively investigated $PETCO_2$ data of patients with a meanPAP >25 mmHg at rest, due to chronic left heart (LH-PH), and pulmonary disease (Lu-PH) or CTEPH. $PETCO_2$ was measured at rest and during maximal exercise. Mean values were compared by ANOVA and multiple comparisons were performed with Scheffé equation as post hoc test.
Results: N= 46 patients were included (LH-PH: n= 14, mean PAP 40±11 mmHg, PVR 327±188 dyn s cm^{-5}, PAWP 21±5 mmHg; Lu-PH: n=15, meanPAP 34±8 mmHg, PVR 441±266 dyn s cm^{-5}, FEV1%pred. 63±27; CTEPH: n=17, meanPAP 46±11mmHg, PVR 732±308 dyn s cm^{-5}). $PETCO_2$ at rest was 4.97±1.04 mmHg, 4.70±1.19 mmHg, and 3.55±0.71 mmHg in LH-PH, Lu-PH and CTEPH patients. The PETCO2 difference between LH-PH and CTEPH was 1.38 (CI 95% 0.48 to 2.29 p=0.001), and between Lu-PH and CTEPH 1.14 (CI 95% 0.24 to 2.04 p=0.007).Comperable similar results were obtained with $PETCO_2$ during maximal exercise.
Conclusion: PH caused by CTEPH is characterized by lowered $PETCO_2$ as compared to PH due to chronic heart or lung disease.

P962
Human pentraxin 3 (PTX3) as a novel biomarker for the diagnosis of pulmonary arterial hypertension
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Background: Although inflammation is an important feature of pulmonary arterial hypertension (PAH), the usefulness of local inflammatory markers as biomarkers for PAH is unknown. In this study, we tested plasma concentrations of human pentraxin 3 (PTX3), a local inflammatory marker, would be a useful biomarker for detecting PAH.
Methods: Plasma PTX3 concentrations were evaluated in 50 PAH patients (27 with idiopathic PAH, 17 with PAH associated with connective tissue disease (CTD-PAH), and six with congenital heart disease), 100 age and sex-matched healthy controls, and 34 disease-matched CTD patients without PAH. Plasma concentrations of B-type natriuretic peptide (BNP) and C-reactive protein (CRP) were also determined.
Results: Mean PTX3 levels were significantly higher in all PAH patients than in the healthy controls (4.40±0.37 vs. 1.94±0.09 ng/mL, respectively; $P < 0.001$). Using a threshold level of 2.84 ng/mL, PTX3 yielded a sensitivity of 74.0% and a specificity of 84.0% for the detection of PAH. In CTD-PAH patients, mean PTX3 concentrations were significantly higher than in CTD patients without PAH (5.02±0.69 vs. 2.40±0.14 ng/mL, respectively; $P < 0.001$). There was no significant correlation between plasma levels of PTX3 and BNP or CRP. Receiver operating characteristic (ROC) curves for screening PAH in patients with CTD revealed that PTX3 (area under the ROC curve 0.866) is superior to BNP. Using a PTX3 threshold of 2.85 ng/mL maximized true-positive and false-negative results (sensitivity 94.1%, specificity 73.5%).
Conclusion: Plasma concentrations of PTX3 are more excellent than BNP in the detection of PAH, especially in patients with CTD.

P963
Acute vasoreactivity testing with sildenafil vs nitric oxide in patients with PAH
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Introduction: Vasoreactivity testing with inhaled nitric oxide (iNO) is recommended in patients with pulmonary arterial hypertension (PAH) because of therapeutical and prognostic implications. Sildenafil is a promising agent for acute vasoreactivity testing since it is more stable and easier to handle than iNO. But it is not known if the acute responses to sildenafil and NO are equal.
Objectives: The aim of this study is to compare acute vasoreactivity in response to sildenafil vs iNO in patients with PAH.
Methods: In this retrospective, open-label, and single-centre study we included all patients who were admitted to our adult pulmonary hypertension unit from 2002 to 2011, met the criteria for PAH, and underwent vasoreactivity testing with iNO and sildenafil.
Results: 198 patients were included. 9.6% of the patients met the responder criteria (as defined by the current guidelines) for iNO and 11.6% for sildenafil. Intra-individually, the responses in mPAP and cardiac index (CI) after sildenafil and NO administration correlated (r_{mPAP}= 0.516, $p<0.001$, r_{CI}=0.521, $p<0.001$). At mean there was a significantly higher CI after sildenafil than after iNO application (CI_{NO}=2.40±0.69l/min/m^2; $CI_{sildenafil}$=2.56±0.76l/min/m^2). Applying the current response criteria, the sensitivity to detect NO-responders by sildenafil vasoreactivity was 81.3%, the specificity was 94%, the positive predicitive value was 56%.
Conclusions: In PAH patients the vasoreactive response to sildenafil is stronger than to iNO. The intra-individual vasoreactive responses to both drugs correlate. The sensitivity to detect NO-responders by using sildenafil for vasoreactivity testing was moderate, but the positive predictive value was low.

P964
The clinical role of routine non-invasive parameters in the diagnostic work-up of patients with risk for pulmonary hypertension
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Objective: Pulmonary hypertension (PH) is diagnosed by right heart catheterization. Doppler Echocardiography is the most specific non-invasive screening tool, but the role of other routine measures in the diagnostic work-up of patients is not clearly defined. We hypothesized that a diagnostic algorithm using a combination of simple non-invasive parameters might help to identify patients with PH.

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Patients and methods: We retrospectively analyzed all patients who received a right heart catheterization and a routine non-invasive assessment between 2005 and 2010. The pretest probability for PH was 50%. As first step, the ratio of the S and R waves in lead I of the ECG were determined; a value ≥1 (≥90°) was considered as right axis deviation (RAD). In a second step, further simple non-invasive parameters were analyzed by logistic regression for their association with PH.
Results: We included n=395 patients. RAD was present in n=87 of them. Within these, n=82 had PH, and n=5 did not, revealing a positive predictive value of 94%. In the remaining n=308 patients, we identified n=60 patients with a combination of NT-proBNP<393pg/ml, DlCOcSB>65%, arterial SO2≥95% and Borg dyspnoe score< 3 at the end of six-minute walk test, of which only n=4 suffered from PH revealing a negative predictive value of 93%.
Conclusion: Our retrospective analysis on a large, heterogenous cohort of subjects including patients with and without PH suggests that the combination of simple, non-invasive parameters allows a reliable identification of subjects both with a very high and with very low probability of PH. Further validation in prospective, population based studies is needed.

P965
Patients', relatives' and practitioners' views on pulmonary arterial hypertension
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Purpose: To study practitioners', patients', and relatives' views regarding pulmonary arterial hypertension (PAH) and identify potential improvements in medical care strategies.
Methods: A qualitative study based on semi-structured interviews involving 16 patients, 4 relatives, and 9 practitioners.
Results: Patients, relatives, and physicians have divergent perspectives on PAH. The discrepancies identified concerned their perceptions of the illness and its impact on patients' daily lives. Patients had a broader view, including social, identity, financial, and functional dimensions of PAH impact on their lives, while practitioners' views were more focused on functional aspects. The study also pointed out divergent approaches among physicians to assessing patients' New York Heart Association functional class. The expectations of patients, relatives, and physicians also differed. Patients expected improvement in PAH diagnosis and better coordination between primary care physicians and PAH medical centers. They also valued reduction of side effects, less restrictive medications, and greater consideration of their views in the medical decision making process. Physicians' expectations focused more on identifying and validating therapeutic strategies.
Conclusion: Our results suggest several potential improvements in patient management especially in order to obtain more consensual treatment and to achieve a more uniform approach of PAH functional impact assessment process. The findings may also be useful for enhancing therapeutic education for patients and their relatives. Finally, this qualitative database may help develop patient-reported outcome measures with better content validity.

P966
A slower life in a smaller world. Patients' perspective on living with pulmonary arterial hypertension
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Background: The pulmonary arterial hypertension (PAH) patient management pathway is often defined from the clinician or commissioner perspective. We wanted to gain an in-depth understanding of the patient self reported experience living with PAH.
Objectives: Working to understand how a diagnosis of PAH impacts a patient's life. Exploring the journey through first symptoms to specialist care and the 'life changes' needed.
Methods: Over 1000 General Practitioners were approached to put forward patients with PAH to participate in semi-structured, in depth qualitative interviews designed to determine the key themes emerging from the individual experiences of PAH. Interviews were audio-recorded for subsequent analysis using interpretive phenomenological analysis methodology.
Results: A total of 8 patient interviews were analysed who had the following underlying aetiologies: IPAH (n=3) and ACHD (n=5), aged between 30 – 70 years and treated with different targeted PAH therapies. Patients interviewed were being managed at 4 different PAH Specialist Centres in the UK. Areas where patients' needs were perceived not to be met by healthcare delivery included: 1) patient information materials did not cover PAH impact on co-morbidities, 2) dealing with a crisis on their own, 3) effective counseling when treatment fails, 4) securing disability allowance, 5) being able to live a normal life, 6) minimising the impact on their family.
Conclusions: Specific areas have been highlighted where healthcare delivery does not meet patients' needs. Living with a rare disease has its own unique challenges requiring careful consideration with potential to further improve the patient experience.

P967
Exhaled nitric oxide in reactive pulmonary hypertension
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Background: Pulmonary hypertension (PH) frequently complicates heart failure. In some patients, pulmonary vessels undergo reactive changes due to the chronic elevation of the left ventricular pressure, resulting in severe pulmonary hypertension and increased transpulmonary gradient (TPG). There is evidence that nitric oxide (NO) synthesized by the respiratory epithelium plays a role in the regulation of pulmonary artery pressure.
Aims and objectives: To evaluate whether exhaled NO has a role in reactive PH
Methods: Seven patients with reactive PH (rPH) were compared to 14 patients with passive PH (pPH) and to 15 control patients without PH. All the patients underwent heart catheterization, lung function tests and exhaled NO (FENO), assessed at multiple flow-rates. Alveolar NO and bronchial NO flux (J'awNO) were calculated using the slope–intercept model.
Results: The results are displayed in the Table.

Comparison of haemodynamics, lung function and J'awNO among CP, rPH, pPH patients

	CP	rPH	pPH
TPG ratio	8.27±0.70	20.71±2.41*§	9.57±0.80
Pcwp mmHg	11.73±1.07	25.33±3.16*	23.64±1.64
FEV1/VC%	74.51±2.73	63.50±4.10*	71.84±2.56
FEF50%	69.91±12.46	29.14±4.99*§	52.08±6.94
TLCO%	67.93±6.97	38.00±8.71*§	65.14±4.42
J'awNO nL/min	99.88±17.14	24.17±7.63*§	89.83±16.07

*Significantly different from CP; §significantly different from PHp.

Patients with PHr had significantly lower FEV1/VC% ratio, lung diffusion (TLCO) and J'awNO. J'awNO was closely inversely related to TPG (r=0.385, p=0.032).
Conclusion: It is still unknown why some patients develop severe and/or fixed PH with the same degree of elevated left-sided filling pressure. Our findings suggest that decreased bronchial NO flux and lung diffusing capacity may contribute to reactive PH.

P968
Unique hemodynamic profile of HIV patients with portal hypertension: Comparison with HIV-associated PAH and porto-pulmonary hypertension
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Introduction and objectives: HIV-associated PAH (HIV-PAH) and porto-pulmonary hypertension (PoPHTN) have well described cardiopulmonary profiles. However, little is known about the hemodynamic characteristics when both conditions coexist (HIV-PoPHTN). We hypothesise that in these cases right heart catheterisation (RHC) findings differ from those with HIV-PAH and PoPHTN alone.
Methods: We performed a retrospective analysis of consecutive patients with HIV-PAH, PoPHTN and HIV-PoPHTN and compared their baseline RHC results: right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), pulmonary artery occlusion pressure (PAOP), cardiac index (CI), pulmonary vascular resistance index (PVRI) and pulmonary artery saturation (PAsat). One-way ANOVA and Student t-test between groups were used for analysis.

Table 1

Variable*	HIV-PAH	PoPHTN	HIV-PoPHTN	p value
RAP (mmHg)	12.4 (6.4)	7.6 (4.3)	13.9 (10.2)	0.001
mPAP (mmHg)	45.5 (16.8)	46.9 (10)	48 (13.7)	ns
CI (L/min/m^2)	2.5 (0.8)	3.4 (1.2)	2.6 (0.8)	<0.001
PAOP (mmHg)	10.2 (3.5)	8.9 (3.2)	10.8 (3.9)	ns
PVRI (Wood/m^2)	13.8 (12.5)	14.8 (14.2)	15.3 (8.2)	ns
PAsat (%)	60 (12)	68 (9)	57 (12)	<0.001

*Mean (SD).

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Results: We identified 93 patients; 37 HIV-PAH, 40 PoPHTN and 16 HIV-PoPHTN. Table 1 presents their hemodynamic characteristics.
Table 2 shows comparisons between two groups.

Table 2

	HIV-PAH vs PoPHTN*	HIV-PoPHTN vs PoPHTN*	HIV-PoPHTN vs HIV-PAH
RAP	<0.001	0.002	–
mPAP	–	–	–
CI	<0.001	0.003	–
PAOP	–	–	–
PVRI	ns	ns	–
PAsat	0.001	<0.001	–

*p value (non-significant omitted for clarity).

Conclusion: HIV-PoPHTN has a similar hemodynamic profile to HIV-PAH. Both groups have worse RV function compared to PoPHTN.

P969

Cardiac index by thermodilution and from non-invasive pulse pressure profiles analysis in PAH

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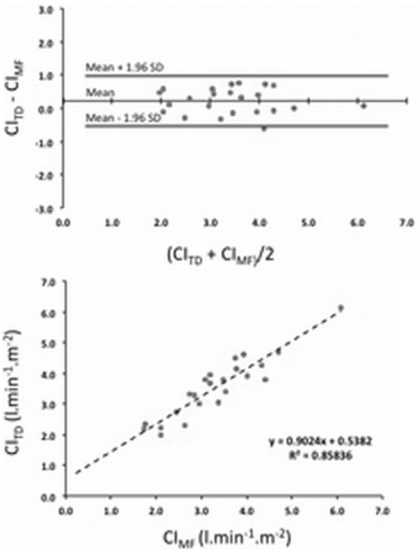
Background: Cardiac index (CI) is an essential parameter to assess severity of pulmonary arterial hypertension (PAH). It is usually measured by thermodilution (TD) during right heart catheterization (RHC).
Aim: We aimed to compare CI measured in PAH patients by RHC to Modelflow© (MF) method from non-invasive fingertip pulse pressure profiles, testing the hypothesis that MF is reliable for CI evaluation in PAH.
Methods: We simultaneously determined CI at rest by TD (CITD) and MF (CIMF) in 22 consecutive patients diagnosed with PAH. Cardiac output (CO) was the mean of 3 values for TD and 100 beat-by-beat values for MF. CI was calculated as CO/body surface area.
Results: Clinical and RHC data are reported in the table. The figure shows (right) CITD as a function of CIMF (Regression line: y = 0.9024x + 0.5382, R^2 = 0.86) and (left) a Bland–Altman analysis (Mean: 0.22; limits of agreement: -0.56 and +0.99).

Clinical and Hemodynamic characteristics

Age, yr	48.2±16.1
Sex ratio, F/M	1.75
Right atrial pressure, mmHg	5.8±3.2
Pulmonary artery mean pressure, mmHg	49.9±15.8
Pulmonary capillary wedge pressure, mmHg	9.3±4.1
Cardiac index by Thermodilution, l/min/m^2	3.3±1.0
Cardiac index by Modelflow, l/min/m^2	3.5±1.0
Pulmonary vascular resistance, Wood units	8.0±4.7



Conclusion: As previously reported for healthy subjects, MF could be usefull for CI estimation in PAH but a calibration against a reference method is required.

P970

Heart rate variability: Possible implications for management of pulmonary arterial hypertension patients

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The aim: to study heart rate variability (HRV) and its relationships with pulmonary hemodynamics and level of NT-proBNP in pulmonary arterial hypertension (PAH) patients.
Material and methods: 6 patients with idiopathic PAH and 3 with congenital heart disease associated PAH with (mean age 31±12 years, 7 patients with FC II and 2 patients with FC III by NYHA/WHO) were enrolled. All subjects underwent right heart catheterization. Level of NT-proBNP was determined in blood. The short-time ECG records obtained in supine position and during orthostatic test were analyzed with Poly-Spectrum software (Neurosoft, Russia). Nine healthy subjects served as a control.
Results: Severe pulmonary hypertension was found in all patients with mean pulmonary arterial pressure 53±14 mmHg, resting pulmonary vascular resistance 1180±650 dyn s cm^{-5}. Total power of PAH patients ranged from 150 ms2 to 2540 ms2 with the very low frequency and low frequency bands predominance in the spectral structure. The orthostatic test caused dramatic lowering in all HRV indexes in PAH subjects. Borderline values of NT-proBNP (up to 400 pg/ml) in PAH subjects were accompanied by some decrease in HRV. Simultaneously, significantly increased NT-proBNP levels (400-3200 pg/ml) were associated with marked HRV lowering both in supine position and during orthostatic test.
Conclusions: Patients with severe PAH were shown with individual various range of HRV parameters, correlating with the level of a neurohumoral activation marker NT-proBNP. HRV can be used in clinical practice to monitor progression of right-sided HF and, consequently, to determine prognosis in PAH patients.

P971

Impact of a wireless implanted pulmonary artery pressure monitoring system in heart failure patients with comorbid chronic obstructive pulmonary disease

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Introduction: Chronic obstructive pulmonary disease (COPD) is a common co-morbidity for heart failure (HF) patients. The presence of high pulmonary artery pressures (PAP) are independently associated with COPD and HF exacerbations.
Objectives: We performed a retrospective analysis to evaluate if PAP monitoring and therapy reduced HF hospitalizations (HFH) in HF patients with a medical history of COPD and/or receiving COPD therapies.
Methods: The CHAMPION trial enrolled 550 patients with NYHA class III HF who were followed for an average of 15 months. In the treatment group, clinicians used PAP data to guide therapy decisions in addition to standard of care versus standard of care alone in the control group.
Results: In the entire CHAMPION cohort, treatment had a 37% reduction in HFH rates (0.46 vs. 0.73, HR 0.63, 95% CI 0.52-0.77, p<0.0001, Anderson-Gill). In the subgroup of 187 patients with comorbid COPD, treatment had a 41% reduction in HFH rates (0.55 vs. 0.96, HR 0.59, 95% CI 0.44-0.81, p=0.0009). Reductions in PAP were analyzed using an area under the curve (AUC) methodology. Overall, treatment had an average AUC reduction of 201.5 mmHg days compared to an increase of 106.5 mmHg days in control (p=0.0299, ANCOVA). In the COPD subgroup, treatment had an average reduction of 353.1 mmHg days compared to a reduction of 57.0 mmHg days in control (p=0.3687).
Conclusions: HF patients with COPD experience high HFH rates but have pronounced benefit from PAP monitoring. Further investigations that analyze the relationship between PAP, COPD, and HF and its implication towards new treatment strategies are warranted.

P972

Is nailfold videocapillaroscopy a valuable diagnostic tool in pulmonary hypertension?

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Background: Pulmonary hypertension (PH) can be based on idiopathic pulmonary arterial hypertension (iPAH), connective tissue diseases such as systemic sclerosis

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(SSc-PAH), left heart disease (LHD-PH), chronic obstructive pulmonary disease (COPD-PH), or chronic thromboembolic events (CTEPH).
Objectives: Analysis of microvascular patterns of patients with PH has been performed using nailfold videocapillaroscopy (NVC). The benefit of NVC in PH was evaluated with focus on SSc patients.
Methods: NVC was performed in 81 patients. 2nd-5th fingers were bilaterally analyzed. Pictures were scored for capillary density (CD, capillaries/mm), and dimensions. Parameters such as hemorrhages and neoangiogenesis or capillary alterations such as ectasia (>20μm) and giant shape (>50μm) were qualitatively assessed.
Results: 14.8% had iPAH, 14.8% LHD-PH, 7.4% COPD-PH and 17.2% CTEPH. 45.7% had SSc and 12.3% SSc-PAH. The CD in SSc-PAH was significantly lower compared to all other PH forms (4.9 vs. 10.2, 10.0, 11.7 and 9.47 in iPAH, LHD-PH, COPD-PH and CTEPH; $p<0.0001$), but did not differ compared to SSc non-PAH (4.7; $p=0.73$). In general, capillary dimensions were larger in SSc-PAH ($p<0.0001$). Ectasias were very common in SSc-PAH (90%), but to some extent present in other forms (e.g. COPD-PH 71.4%). Giant capillaries were only present in SSc (84.6% and 70%). Hemorrhages occurred in all disease forms of this study, mostly in COPD-PH (85.7%) and SSc (80%).
Conclusions: Assessing capillary density in PH is a powerful tool to discriminate between SSc-PAH and other forms of PH. In this respect, NVC should be considered, besides checking for antinuclear antibodies, if the underlying cause of PH is unclear to determine SSc-PAH.

P973
Right ventricular global strain and right ventricular dyssynchrony can predict success to pulmonary vasodilators therapy in PH patients
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Background: Transthoracic echocardiography (TTE) is used to evaluate right ventricular (RV) function in pulmonary hypertension (PH) patients. RV function is assessed using TAPSE or RV end-diastolic area/LV end-diastolic area ratio (RVEDA/LVEDA). RV speckle tracking strain can quantify regional contraction. Pulmonary vasodilators can improve functional status and prognosis but their effects on RV function are poorly described. The aim of our study is to test whether response to pulmonary vasodilators can be predicted by change in RV regional strain.
Methods: 16 patients were prospectively included. They underwent right heart catheterization, usual and 2D strain TTE at baseline and after 3 months of pulmonary vasodilators: PDE5 inhibitors,endothelin receptors antagonists,prostacyclin (single or combination therapy). Success or failure to pulmonary vasodilators were defined according to the guidelines.
Results: At baseline:MPAP was 44*m*11 mmHg, PAPO 11*m*3 mmHg, cardiac index 3.06±0.73 L/min/m^2, RVEDA/LVEDA 1.03±0.43, RV global strain: 12.29±5.34% and RV dyssynchrony: 124±78 msec. A change in global RV strain higher than 70% (-100 to 122%) could predict success to pulmonary vasodilators with a specificity of 100%, a change in RV dyssynchrony of 96 msec could predict success to treatment with a sensitivity of 100%. Change in TAPSE or RVEDA/LVEDA were not accurate enough to predict response to pulmonary vasodilators.
Conclusion: Success to pulmonary vasodilators therapy in PH patients can be predicted by changes in regional right ventricular contraction using longitudinal right ventricular strain and right ventricular dyssynchrony analysis.

P974
Role of C-terminal pro-endothelin in pulmonary hypertension
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Introduction: The endothelin pathway is upregulated in various forms of pulmonary hypertension. Its disease promoting activity has lead to the development of endothelin receptor blockers as specific therapeutics. The highly unstable active form requires greatest care in sample preparation to acquire reproducable results. In this study we examined the role of the more stable CT-proET in pulmonary hypertension using a high precision and standardized system.
Methods: We examined 36 patients retrospectively. Therapy was applied following contemporary guidelines. Samples of platelet free EDTA plasma were stored at -80°C since collection between 2000 and 2003. Biomarker levels were determined by a Kryptor compact (BRAHMS, Germany) according to vendor instructions.
Results: Patients were categorized according to DanaPoint classification as class 1 (n=16), class 2 (n=1), class 3 (n=9), class 4 (n=8) and class 5 (n=2). The mean follow-up time was 4.67 years. Survivors had significantly lower levels of CT-proET (53.7 [31.2-171.8] vs 91.1 [30.6-151.6] pmol/L, p=0.006). ROC analysis for survival yielded an AUC of 80.8%. The optimized cut-off for survival was determined as 65pmol/L. The log-rank test of Kaplan-Meier-analysis for survival was highly significant (p=0.01) with a hazard ratio of 3.06.
Conclusions: CT-proET was significantly elevated in non-survivors of the follow-up period. Optimized cut-offs at 65pmol/L resulted in a significant Kaplan-Meier-analysis for survival. CT-proET-levels above 65 pmol/L are associated with decreased survival in pulmonary hypertension. CT-proET might be a useful biomarker to determine high-risk patients, while offering the advantage of a stable product of the endothelin cascade.

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