157. Pulmonary circulation: clinical aspects of PAH, PTE and CTEPH

P1494
The development of pulmonary hypertension after first episode of acute pulmonary embolism and related risk factors
Shuai Zhang1, Zhenguo Zhai1, Yuanhua Yang1, Tuguang Kuang1, Chen Wang1,2. 1Respiratory and Critical Care Medicine Department, Beijing Institute of Respiratory Medicine, Beijing, China; 2Respiratory and Critical Care Medicine Department, Beijing Hospital, Beijing, China

Background: Part of patients with acute pulmonary embolism(PE) will develop into pulmonary hypertension(PH) including chronic pulmonary thromboembolic hypertension(CTEPH). Related risk factors need to be addressed to guide clinical practice.

Objectives: To investigate the incidence of PH after PE and related risk factors.

Methods: Consecutive patients diagnosed as acute PE admitted to our institute from 2006 to 2010 were included. All the patients were followed till Dec 2011. During the follow-up, patients with PH showed in echocardiogram, defined as estimated systolic pulmonary artery pressure(sPAP) over 50mmHg, received right heart catheterization to confirm the diagnosis of CTEPH.
P1495
Measurement of gas transfer components using nitric oxide in post pulmonary endarterectomy (PEA) chronic thromboembolic hypertension (CTEPH) patients
Louise Harlow, Katrina Oates, Robert Mackenzie-Ross, Joana Pepka-Zaba.
Respiratory Physiology, Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom

Introduction: Reduced TLCO is frequently observed in CTEPH patients. Previous works using the single value of nitric oxide (NO) to differentiate the diffusion membrane capacity (Dm) and capillary blood volume (Vc) of the components of TLCO. It has been suggested, that TLNO is a more accurate reflection of Dm, due to greater affinity for haemoglobin and independence from Vc. This study uses new technology to measure Dm and Vc, using NO, in a cohort of post PEA CTEPH patients. The aim of the study is to compare the relative contribution of Dm and Vc to the reduction in TLCO.

Methods: We studied 24 CTEPH patients (14-male, 10-female, mean age 56±15) post PEA. Full lung function were performed and TLNO and Dm were measured using single breath for NO and CO on a PPTpro system (Viasys). Vc was calculated using the equation 1/(Dm-DmNO/CO/NO/Vc). Patients with co-existing parenchymal lung disease were excluded from the study. Correlations between variables were looked at using Pearson's.

Results: Both Dm and Vc demonstrated a significant correlation with TLCO. Vc was reduced more than Dm (60%/89% respectively).

Conclusions: TLCO is still reduced post PEA, despite successful de-bulking of proximal obstructions and normal TLC and RV. The method used in this study is able to distinguish between the two components of gas transfer. Vc is more affected than the alveolar component Dm. The new technology offers a simple patient friendly procedure allowing measurements of Dm and Vc. This has the potential for improving our understanding of the different components of gas transfer. Further work is warranted in this area.

P1496
Circulating microRNA signature and its novel involvement in pathogenesis of chronic thromboembolic pulmonary hypertension
Lixian Guo1,2, Jun Cai1, Lei Wang1,2, Lifeng Li1,2,4, Jie Liu1,2,3,4, Yuanhui Yang1,2, Raosen Pang1,4, Zhenguo Zhai1,4, Yan Liu6, Song Gu1,4, Chen Wang5,4, Jun Wang2,4,1 Beijing Key Laboratory of Respiratory and Pulmonary Circulation Disorders, Beijing Chao-Yang Hospital, Beijing, China; 2Department of Physiology, Capital Medical University, Beijing, China; 3Department of Beijing Hospital, Ministry of Health, Beijing, China; 4Beijing Institute of Respiratory Medicine, Beijing Chao-Yang Hospital, Beijing, China; 5Cardiology Center, Beijing Chao-Yang Hospital, Beijing, China

Chronic thromboembolic pulmonary hypertension (CTEPH) is a progressive disease characterized by multiple etiology and mechanism. Circulating miRNA is partially derived from cells affected by disease and therefore can serve as potential biomarker and reflect the pathogenesis of this disease. In present study, we compared miRNA expression in plasma from 10 CTEPH patients and 10 healthy control subjects by microarray, and fourteen miRNAs were indentified to be differentially expressed. Selectively, five of the differentially expressed miRNAs were further validated in an independent 40 pairs of subjects by stem-loop qRT-PCR, among which let-7b and miR-22 were downregulated to about 25% in CTEPH patients. Endothelin-1 (ET-1) and transforming growth factor beta receptor (TGFBR1) was the direct targets of let-7b by reporter assay, and plasma ET-1 level was inversely correlated with let-7b. TGFBR1 was further required for induction of ET-1 in endothelial cells.

P1497
Persistent lung perfusion defect is a risk factor for recurrent venous thromboembolism after pulmonary embolism
Alexis Ferre1,2, Benjamin Planquette1,2,3, Armandine Vial1,2, Antoine Roux1,2, Joseph Emmerich1,2,3, Guy Meyer1,2,3, Olivier Sanchez1,2,3, Université Paris Descartes, Sorbonne Paris Cité, Paris, France; 3Service de Pneumologie et Soins Intensifs, Hôpital Européen Georges Pompidou, Paris, France; 4INSERM U 765, Faculté de Pharmacie, Paris, France; 5Service de Médecine Vasculaire, Hôpital Européen Georges Pompidou, Paris, France

Introduction: Up to 50% of patients with pulmonary embolism (PE) still have lung perfusion defects after 6 months of anticoagulant treatment, but little is known about the risk of recurrence in patients with persistent perfusion defect after an acute PE.

Aim of the study: To assess the risk of recurrent venous thromboembolism (VTE) in patients with persistent lung perfusion defects after a first episode of PE.

Patients and methods: Consecutive patients given at least 3 months of anti-coagulant for an objectively proven first episode of acute PE were included. Ventilation/perfusion (VQ) lung scan was performed 6 to 12 months after the diagnosis of PE. Objectively proven recurrent deep vein thrombosis (DVT) and PE were registered during follow-up. Persistent perfusion defects were defined as a pulmonary vascular obstruction > 10% on the VQ lung scan.

Results: 318 patients (mean age 58±19 years) with an acute PE were included. 63 (19.8%, 95% CI 15.4-24.2%) had persistent perfusion defects. During follow-up (median duration: 51 months [25th 75th percentiles: 27 - 73 months]), 71 patients (22%) had a recurrent episode of VTE. In multivariate analysis, persistent defect (HR 2.22; 95% CI 1.3-3.75; p < 0.0048), unprovoked PE (HR 3.48; 95% CI, 1.96-6.19; p < 0.0001), persistent risk factor for VTE (HR 2.64; 95% CI 1.08-6.48; p<0.0001) and age (60 to 75 years; HR 1.88; 95% CI, 1.03-3.61; p=0.0112) were identified as independent risk factors for recurrent VTE whereas prolonged anticoagulation was a protecting factor (HR 0.19; 95% CI 0.07-0.54; p=0.0001).

Conclusion: Persistent perfusion defect is an independent risk factor for recurrent VTE after a first episode of PE.
Involvement of the pulmonary micro-vasculature in chronic thromboembolic pulmonary hypertension (CTEPH)
Sven Gauwens1,2, Olaf Mercier1,2, Xavier Jais1,2, David Montani1,2
Sophie Matte2, Jean-François Paul1, Vincent de Montpréville1, Elie Fadel2,6, Marc Humbert1,2, Gérald Simonneau2,6, Philippe Dartevelle2,6,7, Peter Dormitullé1,6,18, Department of Pulmonology, Hopital Antoine Béclère, Clamart, France; 2Department of Thoracic Surgery, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France; 3Department of Radiology, Hopital Antoine Béclère, Clamart, France; 4Department of Interneve Chirurgicale Marie Lannelongue, Le Plessis Robinson, France; 5Department of Pathology, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France; 6Faculté de Médecine, Université Paris Sud, Kremlin-Bicêtre, France; 7INSERM U999, Hypertension Arterielle Pulmonaire: Physiopathologie et Innovation Thera- peutique, Centre Chirurgical Marie Lannelongue, Le Plessis Robinson, France

Introduction: Pulmonary endarterectomy (PEA) is the treatment of choice for patients with CTEPH. However, a limited subset of CTEPH-patients present with persistent PH after PEA.

Aims: To assess microvascular lesions and clinical characteristics in CTEPH-patients with persistent PH after PEA.

Methods: We analyzed lung histology available from 8/10 patients with persistent PH after PEA and compared them with 10 randomly selected CTEPH-patients with successful PEA.

Results: Histopathology from 8 persistent PH patients revealed thrombotic lesions, intimal fibrosis and medial hypertrophy in peripheral small muscular pulmonary arteries of all analyzed lungs. 7/8 persistent PH patients displayed moderate pulmonary venous involvement, including intimal fibroses of small pre-septal venules, foci of capillary multiplication, and hemosiderosis. All cases presented hypertrophy of bronchial systemic arteries. Hemodynamic data, exercise testing and medical history exhibited non-significant but by-trend discriminating values between the persistent PH and the successful PEA group for PVR (119.9±154 dyne s cm⁻⁵ versus 82±98 dyne s cm⁻⁵), 6-minute-walk distance (6MWD) (272.8±44 vs 415.3±31m), history of vascular implants (6/10 vs 0/10), and presence of subpleural sepsa on chest scanner (4/10 versus 2/10).

Conclusion: We report conspicuous remodeling of the pre- and post-capillary microvascularity in CTEPH-patients with persistent PH after PEA. Group-related discrepancies of PVR, 6MWD, vascular implant-history, and one radio- logic criterion were observed in CTEPH patients with persistent PH, as compared with CTEPH-patients with successful PEA.

P1498

Inventive protocols of CT pulmonary angiography (CTPA) avoid artifacts in CTEPH-patients with successfull PEA.

The purpose of this study is to evaluate three injection protocols for CTPA to improve the image quality of rPA.

Materials and methods: 24 consecutive patients suspected PE underwent CTPAs using a 64-detector MDCT. Each protocol was started with a 3.5ml/sec.-injection of 100ml of CM (300mgI/ml) via vein in upper limb. Three protocols followed the above CM injection, protocol-1 (P-1) with immediate exposure, protocol-2 (P-2) with exposure after 10 sec.-delayed, and protocol-3 (P-3) with exposure after injection of 30ml saline (3ml/sec.). We observed artifacts regarding rPA, subclavian veins, calcification, and motion. Then an artifact-observed score (AOS) was given 0 to 4 as artifact grade.

Results: Each average of AOS in P-1 was 1.30 ± 0.32 in P-2, 0.25 in P-2, and 0.13 in P-3. The AOS in P-1 was higher than the others, in P-2 (p=0.04) and in P-3 (p=0.001). Each average of AOS in subclavian veins and motion artifact did not differ from P-1 to P-3. The CM-density of all regions of interest in P-1 were higher than the others significantly.

Conclusion: These inventive protocols are useful to reduce the artifacts in rPA. They may improve detectability of thrombi in rPA in CTPA.
P1505

Circulating endothelial cell levels decrease after vasodilator therapy and are a biomarker of clinical worsening in refractory pulmonary hypertension in children

Marilyne Levy1, Damien Bonnet1, Laetitia Mauche2, Clément d’Audigier2, David Celermajer3, Pascale Guinseème2, David Smalld1,2, Pediatric Cardiology, Necker Hospital, Université Paris Descartes, Paris, France; 3Hematology, Université Paris Descartes, Carême Paris Cite, France; 4Cardiology and Pneumology Department, Saint Vincent Hospital, University of Sydney, France

Background: Pulmonary vasodilators in general and prostacyclin therapy in particular have improved the outcome of patients with pulmonary arterial hypertension (PAH). Endothelial dysfunction is a key feature of PAH and we previously described that circulating endothelial cells (CECs) could be used as a biomarker of endothelial dysfunction in PAH. We now hypothesized that PAH-specific vasodilator therapy might decrease CEC numbers.

Methods: CECs were quantified by immunomagnetic separation with mAb CD146-coated beads in peripheral blood from children with idiopathic PAH (IPAH, n=30) or PAH secondary to congenital heart disease (PAH-CHD, n=30): before, after treatment and during follow up.

Results: Oral treatment with endothelin antagonists and/or PDE5 inhibitors significantly reduced CEC counts in children. In 10 children with refractory PAH despite oral combination therapy, subcutaneous (SC) treprostinil was added and we observed a significant decrease in CEC counts during the first month of such treatment. CECs were quantified during a 6 to 36 month-follow-up after initiation of SC treprostinil and we found that CEC counts changed over time, with rising counts always preceding clinical deterioration.

Conclusions: CECs might be useful as a biomarker during follow-up of PAH treatment in pediatric IPAH and PAH-CHD, to assess response to treatment and to anticipate clinical worsening.

P1504

Atrial natriuretic peptide as a serum marker of right atrial enlargement and function in pulmonary hypertension

Takahito Sato1, Ichizou Tujino1, Hiroshi Obara2, Noriko Oyama-Manabe2, Masaharu Nishimura3. 1First Department of Medicine, Hokkaido University Hospital, Sapporo, Japan; 2Department of Diagnostic and Interventional Radiology, Hokkaido University Hospital, Sapporo, Japan; 3First Department of Medicine, Hokkaido University School, Sapporo, Japan

Background: Production of atrial natriuretic peptide (ANP) increases in response to right atrial (RA) expansion. However, association between serum ANP level and RA volume has been poorly investigated in pulmonary hypertension (PH). Also, no studies have examined the link between serum ANP levels and RA function.

Methods and results: A total of 51 PH patients were studied. The serum ANP level was 51.6 pg/ml (median, IQR: 31.7 – 121, normal range 0 - 43). Volumetric analysis by cardiac magnetic resonance imaging (CMRI) showed greater RA volume in PH patients (58.6±23 ml/m²) than in 22 controls (40±11 ml/m²) (p<0.001). Analysis of RA function by CMRI indicated similar RA ejection fraction (RAEF) between the two groups; however, fractional emptying and reservoir volume were reduced in PH patients than in controls (p<0.001 for both). Correlation analysis showed significant association between serum ANP levels and RA volume (r=0.45, p<0.001). Serum ANP levels also correlated with CMRI indices of RA function (RAEF: r=-0.66, p<0.001), fractional emptying (r=-0.75, p<0.001) and RA reservoir volume (r=-0.42, p=0.01).

Conclusions: Serum ANP level increases in response to RA enlargement. Importantly, the level is also a marker of reduced systolic and reservoir function of the right atrium in PH.
P1508 Prognostic risk factors of disease worsening in patients with functional class II pulmonary arterial hypertension

Gerald Simonneau 1, Nazzarena Galie 2, Marius M. Hoeper 3, Andjela Kusic-Pajic 4, Jean-Christophe Lemarie 5, Lewis J. Rubin 6, Service de Pneumologie, Hôpital Universitaire de Bicêtre, Université Paris-Sud, Le Kremlin-Bicêtre, France; 2Department of Cardiology, University of Bologna, Italy; 3Department of Respiratory Medicine, Hannover Medical School, Hannover, Germany; 4Clinical Development, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; 5Effi-Stat, Effi-Stat, Paris, France; 6Division of Pulmonary & Critical Care Medicine, University of California, San Diego, United States

Introduction: The open-label extension (OLE) phase of the EARLY trial provides a unique opportunity to analyse long-term data from WHO functional class II pulmonary arterial hypertension (PAH) patients. Here we investigated prognostic factors associated with PAH worsening.

Methods: PAH worsening was defined as initiation of parenteral prostanoids, hospitalization for PAH, initiation of sildenafil, or death. Time to event was defined as time since PAH diagnosis - worsening.

Results: PAH and 22 CTEPH patients were prospectively included. Peak oxygen uptake (VO2 peak) during CPET was 13.6+4 ml/min/kg and 6 minute walk distance (6MWD) was 325±127 m. After multivariate analysis showed an independent association with activity, impact, and total scores in SGRQ and with emotional, physical, social and total scores in MacNew and with mental and physical domains in SF-36. Peak VO2 showed an independent association with all above mentioned subscales in SGRQ and with physical and mental QoL in SF-36, whereas 6MWD was associated with all above mentioned scores of the MacNew and the symptom score of SF36.

Conclusion: Peak VO2 and 6MWD reflect quality of life in patients with PAH and/or CTEPH. In addition, anxiety and depression showed a strong association with mental and physical QoL, underlining the need for awareness of these disorders.

P1510 Potential pharmacological interactions between oral pulmonary arterial hypertension (PAH) therapies and new oral anticoagulants

Jean-Christophe Lega 1, Marc Humbert 2,3, Patrick Missetmi 2,3, 1Thoraxcenter, University of Leuven, Belgium; 2Institute of Experimental Pharmacology, Utrecht, The Netherlands; 3Department of Cardiology, Hôpital Saint-Etienne, Hôpital Nord, Saint-Etienne, France; 4Clinical Pharmacology Unit, CHU Saint-Etienne, Hôpital Nord, Saint-Etienne, France; 5Faculté de Médecine, Université Paris-Sud, Kremlin-Bicêtre, France; 6Service de Pneumologie et Réanimation Respiratoire, Centre National de Référence de l’Hypertension Pulmonaire Sévère, AP-HP, Hôpital Antoine Béclère, Clamart, France; 7U999, Hypertension Artérielle Pulmonaire: Physiopathologie et Innovation Thérapeutique, INSERM, Le Plesis-Robinson, France; 8Department of Internal and Vascular Medicine, Hôpital Lyon Sud, Hospices Civils de Lyon, Université Claude Bernard Lyon 1, France

Background: Anticoagulation with vitamin-K antagonists is currently recommended in PAH. We aimed to search for potential pharmacological interactions between new oral anticoagulants (NOA) and oral PAH therapies.

Methods: We reviewed the potential pharmacokinetic and pharmacodynamics drug-drug interactions (DDI), in particular regarding metabolism and drug transport, for bosentan (B), ambrisentan (A), sildenafil (S), tadalafil (T) and NOA.

Results: B is metabolized mainly by hepatic cytochrome P450 3A4 (CYP3A4), A by uridine 5' diphosphate glucuronosyltransferase and to a lesser extent, by CYP2C19. The organic anion transport proteins for B and P-glycoprotein for both are probably involved in the transports of these drugs. B, but not A, induces CYP3A4, which is involved in the metabolism of anti-Xa NOA rivaroxaban (30%) and apixaban (50%). Concomitant use of B may reduce their biological efficacy. T and S are mainly metabolized by CYP3A4, but act as weak CYP3A4 inhibitors. The risk for clinically significant DDI seems low between S or T and anti-Xa NOA. However, in case of PAH-combination therapy, the risk for decreased concentration might be amplified for anti-Xa NOA. Conversely, an increased risk of myocardial infarction recently evoked with dabigatran, an anti-IIa drug not metabolised by CYP, should preclude its use in PAH.

Conclusion: DDI may occur in PAH patients receiving NOA and PAH therapies, and potentially amplified in case of combination therapy. In the absence of robust clinical and pharmacological data, NOA are not recommended in PAH.
To study pulmonary hemodynamics and the prevalence of porto pulmonary hypertension (POPH) in cirrhotic patients
Sachin Kumar¹, Praveen Kumar Sharma², Manej Kumar Sharma², Ashish Kumar³, Shiv Kumar Sarin⁴, ¹Pulmonary Medicine, Institute of Liver & Biliary Sciences, New Delhi, Delhi, India; ²Hepatology, Institute of Liver & Biliary Sciences, New Delhi, Delhi, India

Background: Pulmonary hypertension (PH) (mean pulmonary artery (MPA) pressure ≥ 25mm Hg at rest) associated with cirrhosis have variable etiologies and prognostic implications.

Aim: To study pulmonary hemodynamics and determine the prevalence of porto pulmonary hypertension (POPH) in cirrhotic patients.

Method: Retrospective study comprised 1492 patients with cirrhosis seen at a tertiary teaching hospital from July 2001 to March 2011 undergoing invasive haemodynamic measurements during hepatic venous pressure gradient (HVPG) study. The data on etiology of cirrhosis, medical history and Child-Pugh classification of liver disease also collected.

Result: 1492 patients(M:F, 1177:315, Child A:B:C, 378:360:754) mean age 45±13.2 years had confirmed PH and 7 (0.47%) patients satisfied the criteria of POPH. Out of 37 PH patients, precapillary PH was present in 7 (POPH group) while postcapillary PH was present in 30 (2.0%) and was passive in 27 patients. Cardiac dysfunction (n=17), spirometric evidence of COPD (n=10 including 4 overlap with cardiac disease), unknown (n=4) and serological evidence of connective tissue disorders (n=3) were also present in postcapillary PH patients. Only 3 out of 30 patients had reactive postcapillary PH (Transpulmonary gradient (TPG) > 12mm Hg). Higher MPA and TPG significantly associated with POPH

Conclusion: The prevalence of POPH in cirrhosis was 0.47%. Presence of PH in cirrhosis should alert the physician to search for more common causes other than POPH, may be more amenable to treatment, making them eligible and also reducing the risk associated with untreated PH, especially in patients being considered for liver transplantation.