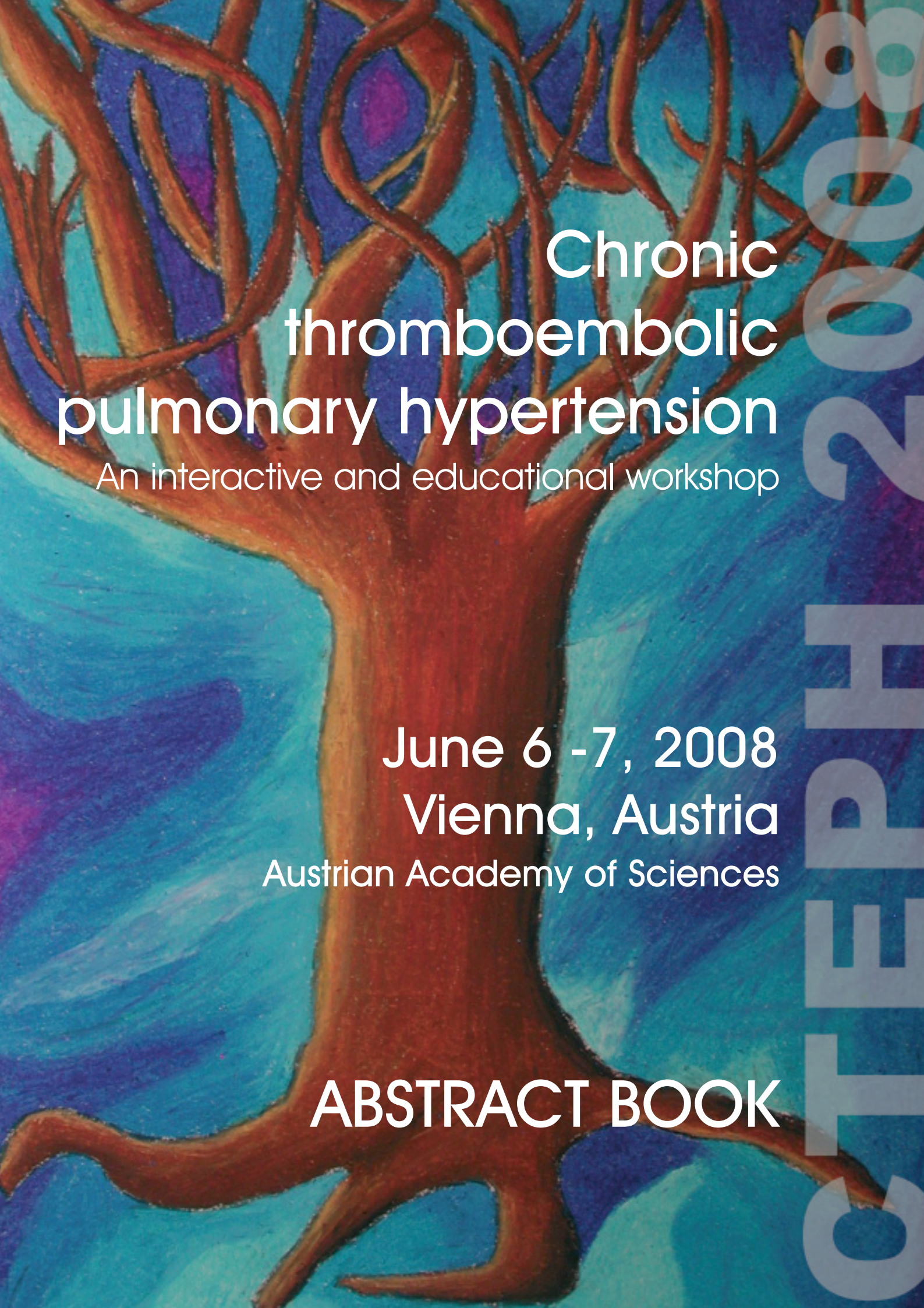

Chronic thromboembolic pulmonary hypertension

An interactive and educational workshop

June 6 -7, 2008

Vienna, Austria

Austrian Academy of Sciences

ABSTRACT BOOK

CTEPH 2008

Content

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endorsed by ÖKG and ÖGP
with support of ESC Working Group on Pulmonary Circulation and RV Function

Friday, June 6 2008

BASIC SCIENCE

Mini-Symosium-1
09.00 – 10.30

01 Major vessel chronic thromboembolic pulmonary hypertension (CTEPH)- the concept of curable pulmonary hypertension

N.H. Kim
(University of California, San Diego)

Chronic thromboembolic pulmonary hypertension represents a two-compartment disease: major vessel, proximal obstructive defect that is surgically treatable, and varying degrees of small-vessel disease with histopathologic features similar to idiopathic pulmonary arterial hypertension. The presence of such small-vessel disease however does not necessarily preclude clinical benefit from surgically removing the proximal chronic thromboembolic material. Accordingly, pulmonary endarterectomy remains the principal treatment in majority of patients with CTEPH. What began as a novel, high-risk treatment has become the cornerstone of CTEPH management. This session will highlight the history and development of our current approach to CTEPH.

02 Thrombosis in the antiphospholipid syndrome

P.G. de Groot
(Department of Clinical Chemistry and Haematology, University Medical Centre Utrecht, the Netherlands)

The antiphospholipid syndrome (APS) is a non-inflammatory autoimmune disease characterized by the presence of antiphospholipid antibodies in the plasma of patients with venous and/or arterial thrombosis and/or recurrent complications of pregnancy. The first case reports that pointed to the existence of antiphospholipid antibodies date back to 1952 but it lasted until 1980 when the correlation between the presence of these antibodies and thrombo-embolic complications was well established. APS is a special syndrome in a number of ways. The clinical manifestations that characterise the syndrome are relatively common and in most cases not caused by the presence of antiphospholipid antibodies. The presence of antiphospholipid antibodies in the plasma of the patients is mandatory to assign the syndrome to a patient. Three different assays are now available to detect the presence of antiphospholipid antibodies (and thus the syndrome), a clotting assay that measures the prolongation of clotting times by the antibodies (lupus anticoagulants, LA) and two ELISAs that measure the presence of anti-anticardiolipin antibodies or anti-$ß_2$Glycoprotein I (b2GPI) antibodies. Of these three assays, LA correlates by far the best with the presence of thrombosis and pregnancy morbidity.
In a LA assay, the presence of aPL is detected by a prolongation of clotting times, results normally used to detect a bleeding tendency. It is difficult to envision how these antibodies that are detected with assays for a bleeding tendency can cause thrombosis. Is there a link between the way the antibodies induce a prolongation of an in vitro clotting assay and the pathophysiology observed in patients with these antibodies circulating in their blood? We have learnd how the presence of these antibodies induces prolongation of clotting tests. The antibodies dimerise $ß_2$GPI, thereby increasing their affinity for negatively charged phospholipids. An important observation was that $ß_2$GPI, dimerised after binding of antibodies, not only has an increased affinity for phospholipids but also for cellular surfaces. In particular increased binding of $ß_2$GPI to endothelial cells, monocytes and platelets have been shown after interaction with anti-$ß_2$GPI antibodies. The interaction of the antibody-$ß_2$GPI complexes results in activation of these cells. A number of receptors have been identified that mediates the activation of endothelial cells, monocytes and platelets by $ß_2$GPI-antibodiy complexes. We now think that the activation of the cells involved in the haemostatic process is the major cause of the observed clinical manifestations.
A model that can explain the pathophysiology might be as follows. Both the autoantibodies and $ß_2$GPI are present in the circulation but they do not interact with each other, because the epitope that is recognised by the antibodies is cryptic, it is not exposed on the outside of the molecule and there are no circulating immune complexes. Only after an injury, when negatively charged surfaces that are normally hidden from the circulation are exposed, $ß_2$GPI can bind. The binding will change its tertiary conformational, allowing the antibodies to bind. The complex has a much stronger affinity for cellular surfaces and the complex stays attached to the cells and will subsequently interact with receptors on the surface of the cell. The interactions of the complex with the receptors will potentate the activation of the cells that has already taken place as the result of the injury. The first step of the process is thus the exposure of an anionic surface. An injury is needed before the autoantibodies can

show their pathological activity, the reinforcement of a normal response to vascular injury.

03 Malignancy and Thrombosis

W. Ageno
(University of Insubria, Clinical Medicine, Varese, Italy)

Cancer is associated with the development of a hypercoagulable state. Tumour cells produce procoagulant factors, such as tissue factor and cancer procoagulant. Tumour specific prothrombotic properties contribute to the process of tumour growth and dissemination. This prothrombotic state makes thromboembolism a well recognized complication of malignant disease. Clinical manifestations vary from venous thromboembolism to disseminated intravascular coagulatioin and arterial embolism. Recent studies have shown that cancer in particular increases the risk of deep vein thrombosis and pulmonary embolism by four to six-fold and patients with malignancy represent about 15-20 % of all patients with acute venous thromboembolism. Furthermore, about 10% of patients presenting with unprovoked or idiopathic venous thromboembolism are diagnosed with early or advanced malignancy within two years of the thrombotic event; hence, approximately one quarter of all venous thromboembolism cases are related to underlying malignancy. Clinical characteristics of acute deep vein thrombosis and pulmonary embolism have been reported to be different in cancer patients compared with patients without cancer; the natural history of venous thromboembolism is usually more aggressive in oncologic patients and the probability of death in cancer patients with venous thromboembolism is higher than in patients with cancer alone or venous thromboembolism alone. Moreover, anticoagulant treatment failure is more frequent in patients with malignancy; a number of recent studies have clearly shown that the risk of recurrences is about two to three-fold higher and the risk of major bleedings two to six-fold higher than in patients without cancer.

04 The interaction of bacterial pathogens with platelets

D. Cox
(Royal College of Surgeons, Molecular and Cellular Therapeutics, Ireland, Dublin)

The interaction of platelets with pathogens plays an important role in the pathogenesis of many infectious diseases. Many bacteria can induce platelet activation which in the case of a focal infection can lead to thrombotic complications while during systemic infection it leads to platelet consumption and thrombocytopenia. Bacteria can activate platelets by secreting activating factors such as proteases or lipopolysaccharide. However, many bacteria can bind to platelets either through a direct interaction with a cell wall associated protein or indirectly through a bridging ligand. Thus, Streptococcus sanguinis binds to platelet GPIbα through its Hsa protein while Staphylococcus aureus clumping factor (Clf) and Fibronectin-binding protein (Fnbp) bind fibrinogen which in turn interacts with GPIIb/IIIa on the platelet surface. These interactions will support platelet adhesion to a bacteria-coated surface; however, they are insufficient to trigger platelet aggregation. For platelet activation to occur a second signal is required and this is provided by bound antibody interacting with FcγRIIa on the platelet surface. This cross-linking of FcγRIIa with either GPIIb/IIIa or GPIbα triggers platelet activation and subsequent aggregation. However, there is also a more generalized mechanism that can support platelet activation even when there is no platelet interacting proteins available. Complement formation on the bacterial surface can provide the second signal as it can interact with complement receptors on the platelet surface providing the second signal in conjunction with FcγRIIa. Thus, FcγRIIa plays a key role in mediating the effects of bacteria on platelet function.

05 Platelets and Thrombosis

S. Panzer, I. Pabinger, C. Ay,
C. Mannhalter
(Medical University Vienna, Austria)

Platelets have an established major role in arterial thromboembolic disease. Their role in venous thrombosis becomes appreciated only recently. Soluble P-selectin (sP-selectin) comes mainly from platelets. This cell adhesion molecule has an important role in the pathophysiology of thrombosis. We show increased sP-selectin concentrations (odds ratio 8.5 (95% CI, 3.7–23.3; P<0.001) in association with venous thromboembolic disease and genotype status. Concentrations of sP-selectin are lower in individuals carrying the P-selectin Pro715 variant than in those without this variant. Likewise, levels of sP-selectin are elevated in patients with lupus anticoagulant and thrombosis compared to those without thrombosis (p=0.0096). The P-selectin Pro715 allele is slightly more frequent

in patients with venous thrombotic disease, but not significantly associated with levels of sPselectin. Thus, in lupus anticoagulant patients, the disease outweighs the genetic disposition. Levels of sP-selectin may be used to the determine individuals' risk for repeat thrombosis.

Mini Symposium-2
11.00 – 12.00

06 Inflammation and Thrombosis
R. De Martin
(Dept. of Vascular Biology and Thrombosis Research, Medical University of Vienna, Austria)

The endothelium plays a key role in vascular inflammation through the expression of chemokines, adhesion molecules and components of the coagulation system leading to e.g., attraction, adhesion and transmigration of cells of the immune system. We have been studying the molecular mechanisms of the inflammatory response, with particular emphasis on the signaling pathways and transcriptional regulators that are involved.
Stimulation of endothelial cells with pro-inflammatory mediators leads to the up-regulation of a large number of genes that contribute to the pro-inflammatory phenotype. However, a substantial number is associated not only with inflammation but relates to proliferation, migration, apoptosis/survival, metabolism, and coagulation. Genes can be grouped according to their kinetics of expression, and these patterns may be controlled by specific (sets of) transcription factors. One transcription factor of central importance is NF-κB, which is common to almost all of the induced genes. Regulation of NF-κB is subject to both positive and negative feedback mechanisms that enable fine-tuning as well as crosstalk with other signaling pathways. Also, a set of genes with negative regulatory function is induced early after pro-inflammatory stimulation, suggesting that shut-down of the inflammatory response is initiated already at quite early stages. These negative feedback mechanisms appear to be operative on several levels, including mRNA stability, receptor internalization, and generation of anti-inflammatory mediators. The expression of genes encoding molecules with negative regulatory function can be considered central for the shut-down of the inflammatory reaction in order to prevent transition to a chronic stage with detrimental effects on the organism.

07 Innate and adaptive immunity in vascular disease
C. Binder
(Department of Medical and Chemical Laboratory Medicine, Medical University of Vienna)

The functional role of the immune system in vascular diseases has gained much attention in recent years, and atherosclerosis in particular has been found to be prominently influenced by immunity. Atherosclerosis is a chronic inflammatory disease in which both dyslipidemia (i.e. especially high LDL cholesterol levels) and inflammation play a key pathogenic role. These inflammatory responses are critically involved at all stages of atherosclerotic lesion formation, which is best exemplified by the fact that moderately elevated levels of highly sensitive measurements of C-reactive protein are an independent risk factor for future coronary artery disease in a healthy population. Moreover, there is increasing evidence that certain immune mechanisms can have a profound modulatory role in atherogenesis. The fact that both innate and adaptive immune responses play an important sometimes even dominant role is demonstrated by scores of examples in which manipulations of certain immune function have profoundly impacted atherogenesis in murine models, accelerating but providing atheroprotective influences as well. Most cellular components of the immune response such as monocyte/macrophages, dendritic cells, T cells, NKT and NK cells, and mast cells are present in lesions. In addition, non-cellular components of immunity are prominently found in established lesions, including complement factors and immunoglobulins, in part bound to specific disease-related antigens, such as oxidized LDL (OxLDL). The functional role of these immune responses in atherogenesis, plaque rupture, and vascular response to injury will be discussed.

08 Progenitor cells and vascular remodeling
W. Speidl
(Medical University of Vienna, Department of Internal Medicine II, Vienna, Austria)

The Zena and Michael A. Wiener Cardiovascular Institute, Mount Sinai School of Medicine, New York and the Department of Internal Medicine II, Medical University of Vienna
Several reports showed that bone marrow derived progenitor cells (BMPC) may participate in neovascularization and re-endothelialization after vascular injury and therefore may play a

crucial role in vascular diseases like atherosclerosis, restenosis and pulmonary arterial hypertension (PAH).
Clinical studies have shown that atherosclerotic risk factors, endothelial dysfunction and an increased risk for vascular events are associated with a decreased number of circulating endothelial progenitor cells. In addition, chronic treatment with BMPC decreased the progression of atherosclerosis in apoE-/- mice. We were able to demonstrate that the prevention of oxLDL-induced apoptosis of BMPC leads to homing of these cells in the necrotic core of atherosclerotic plaques and rapidly increases its stability and reduces its size in apoE-/- mice.
BMPC participate also in repair after vascular injury. Interestingly, the number of neointimal and medial BMPC correlated to the severity of the injury. Modulation of BMPC by growth factors and cytokines have been shown to change neointima size and composition. We could show that inhibition of VEGF after femoral artery wire denudation injury dramatically reduces endothelial repair by BMPC which results in increased neointima formation.
Although endothelial dysfunction or damage may also trigger the pathogenesis of PAH and clinical studies have shown that the number of circulating progenitor cells is reduced in patients with idiopathic PAH and in patients with severe lung disease, the role of BMPC in PAH is controversially discussed. Despite it has been reported that only few endogenous BMPC differentiate into vasculature cells after induction of PAH, treatment with exogenous BMPC have been shown to ameliorate the disease in animal models and in humans.

Oral abstract session
13.30 – 15.00

09 Poly I:C, a double-stranded RNA analog modulates Ca2+ signaling in human pulmonary artery endothelial cells

Z. Bálint[1/5], W.F. Graier[2], K.T. Preissner[3], H. Olschewski[4/5], A. Olschewski[1/5]
([1]University Clinic of Anaesthesia and Intensive Care Medicine,[2] Institute of Molecular Biology and Biochemistry, of the Medical University of Graz, Austria,[3] Department of Biochemistry of the Justus-Liebig-University Giessen, Germany ,[4] Department)

Rationale: In human pulmonary artery endothelial cells (hPAECs) the intracellular Ca2+ represents the main regulator for cell permeability and excitability. Polyinosinic:polycytidylic acid (polyI:C) was reported to mimic the effect of natural double-stranded RNA on intercellular tight junctions in endothelial cells. However, the underlying mechanisms are largely unknown.
Methods: We investigated the effect of polyI:C on the Ca2+ homeostasis in fura-2 loaded hPAECs using live cell imaging. The cells were stimulated with 100µM histamine after incubation for 48h with 25µg/mL polyI:C or control solution.
Results: There was no significant difference in the resting Ca2+ concentration and in the histamine-induced peak Ca2+, independently of treatment and extracellular Ca2+. However, preincubation with polyI:C significantly prolonged the duration of the histamine-induced signal from 69.2±3.5 sec (n=41) to 96.7±4.8 sec (n=29) in the absence of extracellular Ca2+ and from 111.7±16.8 sec (n=33) to 187.6±6.7 sec (n=22) in the presence of extracellular Ca2+.
Conclusion: Our data suggest that polyI:C modulates histamine-induced Ca2+ signaling in hPAECs by affecting Ca2+-extruding pumps, like SERCA or Ca2+-ATPase.

10 Vascular wall remodeling in patients with chronic thromboembolic pulmonary hypertension: a role for c-reactive protein.

M. Wyants, R. Quarck, E. Alfaro-Moreno, B. Meyns, M. Delcroix
(Pneumology, Katholieke Universiteit, Leuven, Belgium; Occupational, Environmental and Insurance, Public Health, Katholieke Universiteit, Leuven, Belgium; Basic Research, Instituto Nacional de Cancerologia, Mexico City, Mexico; Cardiac Surgery, Universita)

CTEPH is associated with proximal vascular obstruction whose origin is not elucidated. Our hypothesis is that in addition to dysregulated thrombosis and/or thrombolysis, uncontrolled inflammation could be involved. Considering that CTEPH patients have elevated CRP levels, our objective is to understand the intercellular mechanisms underlying vascular remodeling in CTEPH. Primary cultures of endothelial (EC) and smooth muscle cells (SMC) were established from large pulmonary vessels of CTEPH patients (n=5). Normal primary human pulmonary artery EC (hPAEC) and SMC (hPASMC) were used as control cells. Migration and proliferation of SMC and adhesion of EC from CTEPH have been compared to hPAEC and hPASMC. EC from CTEPH patients have a 3-fold increased adherence of monocytic cells (U937), in the presence of CRP, compared to hPAEC ($p<0.0001$). Proliferation and migration of SMC from CTEPH patients were 3-fold higher compared to hPASMC ($p<0.05$). EC from CTEPH patients secreted higher levels of endothelin than hPAEC (246±22 vs. 90±6 pg/ml,

p=0.001). SMC proliferation is 1.7-fold enhanced by supernatants of CTEPH patient EC compared to hPAEC (p=0.01). Our results suggest a role of CRP in the vascular remodeling in CTEPH.

11 Prognostic and Aetiological Factors in Chronic Thromboembolic Pulmonary Hypertension (CTEPH)

R. Condliffe[1/2], D.G. Kiely[2], JSR. Gibbs[3], P.A. Corris[4] , A.J. Peacock[5], D.P. Jenkins[1], K. Goldsmith[1], J.G. Coghlan[6], J. Pepke-Zaba[1]
(1)Pulmonary Vascular Disease Unit, Papworth Hospital, Cambridge, United Kingdom; (2) Pulmonary Vascular Disease Unit, Royal Hallamshire Hospital, Sheffield, United Kingdom; (3) Department of Cardiology, Hammersmith Hospital, London, United Kingdom;
(4) Northern Pulmonary Vascular Unit, Freeman Hospital, Newcastle-upon-Tyne, United Kingdom; (5) Scottish Pulmonary Vascular Unit, Western Infirmary, Glasgow, United Kingdom, (6) Department of Cardiology, Royal Free Hospital, London, United Kingdom)

Introduction: Several prognostic variables for CTEPH have previously been identified. Specific medical conditions have also been associated with its development and prognosis. Using a national registry we have assessed the prognostic value of a larger number of variables. We have also attempted to validate the previously identified aetiological factors within a national population.
Methods: Baseline data for all 469 CTEPH patients diagnosed in the UK pulmonary hypertension service during 2001-06 were collected from hospital records.
Results: Gas transfer and exercise capacity below the median independently predicted pulmonary endarterectomy perioperative mortality. Cardiac index and exercise capacity below the median independently predicted poor outcome in non-surgical disease. Previous splenectomy was noted in 6.7% of patients, being significantly more common in patients with non-surgical rather than surgical disease (13.7% v 3.6%, p<0.001). We did not find that medical risk factors were predictive of mortality.
Conclusion: In this large national cohort, novel independent predictors of outcome in patients with both surgical and non-surgical CTEPH have been identified. These may be useful in planning treatment. The aetiological importance of previously identified risk factors has been confirmed, although we have been unable to reproduce their prognostic strength.

12 Submassive pulmonary embolism (SPE)- different therapeutic approaches.

A. Majsnerowska, A. Nowowiejska-Wiewióra., I. Skoczylas, T. Zebik, M. Gierlotka, L. Polonski (Silesian Centre for Heart Disease, Zabrze, Poland)

Introduction: SPE concerns hemodynamically stable patients with right ventricular dysfunction (RVD). The use of thrombolytic agents in treatment of SPE remains controversial. Material and methods: 125 consecutive patients with pulmonary embolism were included in retrospective study. 18 patients with massive PE were excluded. 61 patients had RVD defined as right/left ventricular diastolic diameter ratio >0,6 and/ or RV end-diastolic diameter > 30 mm- fulfilled criteria of SPE. They were divided in two groups based on treatment strategy: Heparin group- H (37 pts, 45,9% men, mean age 52,8); Thrombolysis group- T (24 pts, 58,3% men, mean age 52,2). Results: Clinical and echocardiographical parameters were simmilar in both groups. There were no significant differences concernig in- hospital mortality (H- 5,4%, T- 8,3%, NS), long-term mortality (H- 17,6%, T- 8,3%, NS) and PE recurrences in follow-up (H- 5,9%, T- 4,2%, NS). Bleeding complications were observed more often in T (25% vs. 5,4% in H, p<0,05), however there was no cerebral and fatal bleeding. Conclusion: The results of the study do not support the indication for thrombolysis in SPE. Appropriate therapy in such patients still remains unknown.

13 Preoperative Pulmonary Vasoreactivity in Chronic Thromboembolic Pulmonary Hypertension Patients Undergoing Pulmonary Endarterectomy

F. Mojoli[1], A.M. D'Armini[2], S. Mariconti[1], M. Morsolini[2], V. Emmi[1], M. Viganò[2], A. Braschi[1]
((1)Division of Critical Care, (2)Division of Cardiac Surgery)

Purpose: To analyze the relationship between preoperative response to inhaled Nitric Oxide (iNO) in chronic thromboembolic pulmonary hypertension (CTEPH) patients and the outcome of pulmonary endarterectomy (PEA).
Methods: Nineteen consecutive CTEPH patients, in whom spiral CT excluded a distal pattern, underwent 2 right heart catheterizations: preoperatively to assess basal hemodynamic and response to iNO and postoperatively to assess outcome of PEA.
Results: At pre-PEA hemodynamic assessment, Cardiac Output (CO) was 4.3±1.6 L/min, mean Pulmonary Artery Pressure (mPAP) 45±14 mmHg and Pulmonary Vascular Resistance

(PVR) 826±371 dynes*s*cm-5. Inhaled NO decrease mPAP to 37±10 (-18%) and PVR to 707±304 (-15%). Four patients (21%) were high responders to iNO and 15 patients (79%) were low responders according to a PVR decrease e‟ or < 200 dynes*s*cm-5, respectively. High responders had also higher basal PVR (1213±222 vs. 723±335 dynes*s*cm-5; p<0.01) but not significantly higher PVR during NO inhalation (839±167 vs. 672±327 dynes*s*cm-5) than low responders. PEA decreased mPAP to 25±8 mmHg (-44%), PVR to 248±103 dynes*s*cm-5 (-63%) and increased CO to 5.4±2.0 L/min (+26%). The 4 high responders had worse PEA outcomes: 1 patient experienced severe postoperative pulmonary hypertension and right heart failure, required ECMO and died 4 days after PEA; in the other 3 high responders, mean postoperative PVR was significantly higher than that observed in low responders (370±97 vs. 223±87 dynes*s*cm-5; p < 0.01).
Conclusions: In CTEPH patients, a preoperative high response to NO inhalation may suggest that a significant portion of PVR is not correctable by PEA.

14 Prevalence of chronic thromboembolic pulmonary hypertension 2 years after pulmonary embolism

D. Martí, D. Jiménez, C. Escobar,
I. Rodríguez, M. Sarrión, D. Taboada, M.L. Giganto, G. Díaz, A. Sueiro, R. Yusen
(Ramón y Cajal Hospital, Department of Medicine, Ramón y Cajal Hospital, Department of Medicine, Madrid, Spain)

Background: Studies of chronic thromboembolic pulmonary hypertension (CTPH) may underestimate its prevalence. We aimed to evaluate the prevalence of symptomatic and asymptomatic CTPH.
Subjects and methods: We conducted a prospective, long-term, cohort study in consecutive patients with an acute symptomatic episode of pulmonary embolism (PE) diagnosed by contrast-enhanced PE-protocol multidetector chest CT or ventilation/perfusion scintigraphy (VQ) in the emergency department of Ramon y Cajal Hospital, Madrid, Spain. All patients underwent transthoracic echocardiography and CT or VQ 2 years after the diagnosis of PE. CTPH was considered to be present if the estimated systolic pulmonary artery pressure exceeded 40 mm Hg and there was evidence of residual PE by VQ or CT.
Results: Of the 137 enrolled patients with PE, 18 were excluded because they had conditions potentially responsible for nonthromboembolic pulmonary hypertension (15 had chronic obstructive pulmonary disease, and 1 patient each had asthma, sleep apnea, and congestive heart failure). Of the 119 remaining patients, 26 had CTPH (21.8%, 95% CI 14.8%-30.4%) and only half of these patients were symptomatic. Using logistic regression of multiple baseline covariates, only age (odds ratio, 1.16 per year) was associated with an increased risk of CTPH.
Conclusions: Almost one quarter of patients have CTPH at 2 years after acute symptomatic PE, and only half are symptomatic. Future studies are needed to address the prognostic significance of this finding.

Mini-Symposium-3

15.00 – 16.30

15 TGF-beta signaling and vascular remodeling

N. Morrell
(University of Cambridge School of Clinical Medicine, Department of Medicine, Addenbrooke’s and Papworth Hospitals, Cambridge, UK)

Recent genetic studies have revealed the presence of heterozygous germline mutations in the gene encoding the bone morphogenetic protein type II receptor (BMPR-II) in at least 70% of families segregating familial pulmonary arterial hypertension (PAH). The disease gene penetrance is less than 50%. In addition, 15-25% of patients with idiopathic PAH have mutations in BMPR-II. BMPR-II is a type II receptor in the TGF-ß superfamily of receptors and transduces signals for a number of bone morphogenetic proteins (BMPs). The receptor is expressed on vascular cells and is particularly highly expressed on the endothelium. We have shown that the expression of BMPR-II is reduced in the pulmonary vasculature of patients with familial PAH, but also in patients with PAH in whom no mutation in the BMPR-II gene was detected. Studies in animal models have also confirmed the downregulation of BMPR-II in experimental PAH, and PAH can be prevented in some of these models by overexpression of wild type BMPR-II. Thus a critical reduction in BMPR-II expression and function may be a key feature of diverse forms of PAH. A reduction in BMPR-II expression leads to a reduction in signalling via the Smad1/5 proteins that transduce BMP signals to the nucleus. Pulmonary artery smooth muscle cells (PASMCs) derived from patients harbouring a mutation in BMPR-II are resistant to the growth suppressive effects of BMPs, which may contribute to the abnormal proliferation of

vascular cells that characterise the pathology of PAH. Interestingly, mitogen activated protein kinase (MAPK) pathways converge on Smad1/5 signalling and inhibit nuclear accumulation of the Smad1/5 transcription factors, by phosphorylation of the Smad linker region. Thus growth factors such as platelet derived growth factor or serotonin can further inhibit BMP signalling and may contribute to the „second hit" required for disease manifestation. Some of the major targets of BMP signalling are a group of transcription factors belonging to the inhibitors of DNA binding (Id) family. BMPs fail to induce Id1 and Id2 gene expression in PASMCs from patients with mutations in BMPR-II. Dysregulation of these important transcription factors seems to contribute to the failure of BMP mediated growth suppression in mutant cells. Another important consequence of BMPR-II mutation is to alter the growth response of mutant cells to TGF-ß, which also involves the Id genes. Thus we have defined a key axis in pulmonary vascular cells involving BMPR-II/Smads/Id genes that control vascular cell proliferation and survival. Disruption of this axis leads to abnormal vascular function and proliferation and contributes centrally to the pathogenesis of PAH.

16 Angiopoietin and Notch signaling in pulmonary hypertension

P.Thistlethwaite
(University of California, San Diego, Divison of Cardiothoracic Surgery)

Chronic thromboembolic pulmonary hypertension (CTEPH) develops in approximately 20,000 individuals each year in the United States. It is estimated to result in 3.8% of all cases of acute pulmonary embolism. This disease reflects two distinct pathologic processes: 1) failure of resorption of pulmonary arterial thrombus with adjacent vessel wall remodeling in large pulmonary vessels and 2) a secondary vasculopathy characterized by proliferation of vascular smooth muscle cells and asymmetric neointimal hyperplasia around small pulmonary arteries and arterioles. This small vessel vasculopathy tends to predominate in regions of the lung that are not obstructed by thromboembolism and is remarkably similar to the vascular pathology seen in idiopathic pulmonary arterial hypertension. The dual-compartment pulmonary vascular bed pathology explains the clinical observation that CTEPH patients often have severe pulmonary hypertension out of proportion to the pulmonary vascular obliteration seen on angiography or at the time of surgery.

Our studies focus on changes at the genetic and cellular level that lead to development of small vessel disease in CTEPH and idiopathic pulmonary arterial hypertension. Recent work from out laboratory has shown that Angiopoietin-1, a muscle-secreted angiogenic peptide, and its endothelial-specific receptor, TIE2 play a role in the development of both types of this disease. We have demonstrated that a second receptor signaling system, Notch 3, to be linked to endothelial activation of TIE2 and necessary for the development of small vessel vasculopathy. Our group has demonstrated that: 1) human and rodent pulmonary hypertension are characterized by overexpression of Notch 3 in lung arteriolar smooth muscle cells, and that the severity of disease correlates with the amount of Notch 3 protein in the lung, 2) mice with homozygous deletion of Notch 3 do not develop pulmonary hypertension in response to hypoxic stimulation, 3) pulmonary hypertension can be prevented or successfully treated in rodents using gamma-secretase inhibitor that blocks activation of Notch 3 in smooth muscle cells, and 4) Notch 3 receptor signaling through HES 5 shifts vascular smooth muscle cells to undifferentiated proliferative phenotype. These data suggest that the Angiopoietin and Notch signaling pathways may be crucial for the development of small vessel pulmonary hypertension and provides target pathways for therapeutic intervention.

reflecting both large (proximal) and small (distal) vessel disease may be the key to understanding why not only some patients with longstanding thromboembolic disease develop severe pulmonary hypertension, but also why the degree of pulmonary hypertension is often out of proportion to the degree of vascular bed obstruction

17 Circulating fibrocytes in pulmonary vascular remodelling

V. Nikam[1], G. Hild[2], R. Schermuly[1/2]
R. Dumitrascu[2], N. Weissmann[2], W. Seeger[1/2], R. Voswinckel [1,2]
([(1)]Max-Planck-Institut für Herz- und Lungenforschung, Bad Nauheim, Germany, [(2)]University Giessen Lung Center –UGLC, Department of Internal Medicine, Giessen, Germany)

Objective: Circulating fibrocytes (CFs) comprise a recently described new cell type of blood born derived fibroblast like cells that are recruited from the circulation to sites of wound repair, vascular remodelling or fibrotic tissue remodelling. A role of these cells in the pulmonary vascular remodelling in pulmonary

hypertension has been proposed. Hence, we focussed on these cells type to decipher their role in pulmonary hypertension.
Methods: FACS, confocal laser scanning microscopy; Western blot, qPCR, Rap pull down assay and in vivo hypoxia induced pulmonary hypertension murine model.
Results: We observed that freshly isolated human peripheral mononuclear cells (PBMCs) upon treatment with treprostinil exhibited poor cell adhesion and subsequently reduction of cell differentiation in ex-vivo expansion. Our further investigations indicated a cAMP induced integrin impairment that was a PKA independent process transduced via an alternative cAMP-RAP-ERK axis. We created blood chimeric animals by bone marrow transplantation of wild type C57 mice with bone marrow derived from eGFP mice. We found a significant contribution of these cells to pulmonary vascular remodelling of the chronic hypoxic mouse and this cellular recruitment was inhibited upon treatment with continuous treprostinil infusion in the mouse directed by an implanted minipump.
Conclusion: We could show that prostanoids, which are approved for clinical therapy of pulmonary hypertension, potently inhibit the in vitro differentiation of CF from blood as well as the in vivo recruitment and integration into pulmonary resistance arteries. We thereby showed that CFs are a new therapeutic target in this devastating disease. The further aims are now to more precisely dissect the pathway of prostanoids action on circulating fibrocytes by introducing mutated Rap, Raf and ERK proteins.

18 TRP Channels and Pulmonary Vascular Remodeling in CTEPH

J. Yuan
(University of California, San Diego, Departement of Medicine)

Pulmonary vascular remodeling in patients with chronic thromboembolic pulmonary hypertension (CTEPH) is associated with increased proliferation of smooth muscle cells (SMCs) and myofibroblasts. Upregulated transient receptor potential (TRP) channels and increased Ca2+ influx through store- and receptor-operated cation channels have been implicated in the excessive SMC proliferation in patients with pulmonary arterial hypertension. This study aims at determining function and expression of non-selective cation channels in cells isolated from vascular tissues removed from patients during pulmonary endarterectomy. Cells prepared from endarterectomized tissues of CTEPH patients were cultured from regions proximal and distal to the fibrotic clot. Multiple types of cells were identified based on their distinct morphology and size. Electrophysiological properties of non-selective cation channels were investigated using the patch clamp technique. Large cation currents were present in most of the cells; decrease in extracellular pH significantly attenuated the amplitude of the cation currents. RT-PCR analyses indicated that the cells isolated from endarterectomized tissues expressed high levels of TRPV (TRPV1-4) and TRPM (TRPM-3, -4, and -7) channels. The mRNA expression level of TRPC channels was relatively low in comparison to that in normal pulmonary arterial smooth muscle cells. These results indicate that cells isolated from endarterectomized tissue from CTEPH patients exhibit morphological and electrophysiological heterogeneity. Highly expressed TRPV/TRPM channels in smooth muscle cells and myofibroblasts may play an important role in the development of pulmonary vascular remodeling in CTEPH patients.

Moderated poster session

17.00 – 18.30

P01 Persistent dyspnea complaints at long-term follow-up after an episode of acute pulmonary embolism: results of a questionnaire

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Background
Information on long term complications of PE, including chronic complaints of dyspnea, is lacking. Methods Consecutive patients with a history of PE and a matched control group with no such history were presented with a questionnaire, designed to establish the presence, severity and possible causes of dyspnea in the clinical course of PE. Results The questionnaire was taken in 48 PE-survivors 40 months after PE; 27 patients (56%) had complaints of dyspnea. Sixteen (35%) were categorized as NYHA class II, 6 (13%) as class III and 5 (10%) as class IV. Overall, 19 patients (70%) had new or worsened complaints after PE. The study included 61 controls. The controls were significantly less dyspnoeic compared to the PE survivors ($p<0.001$). Patients were 4 times more often in NYHA class II (OR 3.6 95%CI 1.4-9.7) and 7-fold more often in NYHA class III or IV (OR 6.5 95%CI 1.7-24). Conclusion A large percentage of PE patients

have persistent complaints of dyspnea at long term follow-up. The majority of them developed new or worsened dyspnea. In comparison to a control population, PE patients were overall significantly more dyspnoeic.

P02 Plasma N-Terminal Brain Natriuretic Peptide in patients with chronic thromboembolic pulmonary hypertension before and after Pulmonary Endarterectomy

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Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is often an ominous disease leading to progressive right heart failure. Selected patients with proximal lesions can be treated by pulmonary thromboendarterectomy (PEA). High plasma brain natriuretic peptide level (NT-proBNP) has been shown to be related to the right heart dysfunction and worse prognosis in patients with pulmonary hypertension (PAH). The aim of our study was to investigate whether NT-proBNP level could reflect clinical and right ventricular function changes at follow up after PEA.
Methods: Thirty CTEPH patients (22 male and 8 female, mean age 53.4 ± 11.9 years, range 27-70yr) with baseline mean PVR 760.4 ± 251.3 dyne •s •cm-5, preoperative WHO functional class 3.0 ± 0.5 and six minute walk distance 368 ± 119.8 m underwent PEA and were followed for a mean of 24.2 months (range 1-84 months).
Results: Significant clinical and echocardiographic improvement was noted as a result of PEA. Also, NT-proBNP concentration decreased from 2503.8 ± 2275.9 pg/mL to 520 ± 740 pg/mL, p<0.0001. The change in NT-proBNP level correlated with decrease of RV diastolic dimension assessed with echocardiography (r=0,49, p=0,005).Among directly assessed hemodynamic variables preoperative NT-proBNP level correlated only with cardiac output (r= -0,48, p=0,011). In contrast correlation with several echocardiographic variables was found: RV diastolic dimension (r=0.58, p=0,001), RV/LV diastolic dimension ratio (r=0.43, p=0.016), tricuspid valve peak gradient (r=0.40, p=0,026) and RV acceleration time (r= -0,48, p=0,016).
At follow up NT-proBNP maintained its correlation with RV diastolic dimension (r=0,38, p=0,034), RV/LV diastolic dimension ratio (r=0.38, p=0,035) and RV acceleration time (r= -0,46, p=0,01) but no longer with tricuspid valve peak gradient. Positive correlation between WHO functional class (r=0,45, p=0,023), arterial saturation at rest (r=-0,51, p=0,006) and 6MWT distance (r=-0,54, p=0,002) were also found.
Conclusions: Preoparative serum BNP seemed more related to the morphology of the heart as assessed by echocardiography then to directly measured, instantaneous hemodynamics. NT-proBNP reflected the beneficial effects of PEA in a whole studied group and correlated with the degree of reverse RV remodeling in individual patients. Interestingly, NT-proBNP seemed also useful for stratifying patients according to long term effects of PEA: At follow-up it retained correlations with RV echocardiographic variables and showed relationship with functional status of patients NT-proBNP is a promising marker in patients qualified for PEA, but reliable assessment of its value requires larger studies.

P03 Patients with chronic thromboembolic pulmonary hypertension (CTEPH) after pulmonary endarterectomy (PEA), in-hospital results

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Introduction: CTEPH concerns almost 1-5 % patients after acute pulmonary embolism. It is probably connected with clot remodeling in proximal parts of pulmonary arteries as well as distal vasculopathy. The PEA is a surgical treatment, which decreases pressure in the pulmonary artery and enhances functional outcome in patients with severe CTEPH.
Material and methods: The inclusion criteria were class III or IV according to the New York Heart Association (NYHA), pulmonary vascular resistance (PVR) > 200 dyn/s/cm-5, proximal changes in pulmonary arteries (classified in 1st or 2nd class according to Jamieson and Kapelanski) without any history of fatal illness such as cancer or irreversible changes in lungs. 30 patients fulfilled inclusion criteria, were protected with the use of vena cava filter prior to the operation and underwent PEA. Two of them died in the first 24 hours after the surgery.
Results: The echocardiographical (right ventricular ejection fraction, right ventricular diameter, tricuspid regurgitation) and hemodynamic measurements (mean pulmonary artery pressure, PVR) as well as

NYHA classification improved significantly($p<0.05$) in all patients.
Conclusion: The PEA not only enhanced patients' outcome but also improved studied parameters significantly. Surgical treatment in CTEPH is beneficial especially in selected patients with proximal arterial clot-vasculopathy.

P04 Improved outcome in medically treated post pea residual pulmonary hypertension

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Pulmonary endarterectomy (PEA) is the standard therapy for eligible patients with chronic thromboembolic pulmonary hypertension (CTEPH). However, in approximately 15% of operated patients residual PH due to a secondary peripheral arteriopathy complicates the successful outcome after PEA. The availability of the disease-modifying medical therapy has changed the management. We describe a case of postPEA PH with substantial improvement following treatment with endothelin receptor antagonist bosentan.

Case report. A 32-year-old man with inherity thrombofilia (APC resistance) following recurrent venous thromboembolism developed severe CTEPH (meanPAP 50mmHg) with segmental obstructions. He underwent PEA without complications. Immediately after PEA a substantial decrease of PH (meanPAP 28mmHg) was revealed, however early symptomatic and hemodynamic (meanPAP 36mmHg) decline occurred. Therapy with bosentan was initiated. After 6 months improvement of hemodynamic and clinical parameters was detected: increase of cardiac index (+ 0,9l/min/m2) and of exercise tolerance (+ 43m in 6MWD), right-ventricle failure moderated.

Conclusion. Although PEA is recommended as the first choice of treatment in CTEPH, ongoing remodelling of peripheral vessels in a small subset of patients is responsible for postsurgery residual PH leading back to right-ventricle pressure overload. Novel medical therapy positively modifies the outcome as in the reported case.

P05 Functional outcome after pulmonary endarterectomy in patients with chronic thromboembolic pulmonary hypertension

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Introduction. Chronic thromboembolic pulmonary hypertension (CTEPH) is potentially correctable form of chronic pulmonary hypertension. Hemodynamic improvement after pulmonary endarterectomy (PEA) is usually associated with improvements in functional class and exercise capacity. The six-minute walk test (6MWT) is frequently used to measure outcomes after treatment in patients with pulmonary hypertension. We studied functional outcome after PEA in patients with CTEPH Patients and methods. Data of 45 consecutive patients (27 males, mean age 54 years, mean pulmonary artery pressure 55±10 mmHg, mean ´pulmonary vascular resistance 11,34±3,58 WU) with CTEPH before and after PEA were analyzed. Patients were functionally classified according to the NYHA classification before surgery, 6, 12 and 24 months after PEA. 6MWT was performed before PEA and 6, 12, and 24 months after PEA.
Results. Preoperatively, NYHA class distribution was respectively 3-II, 38-III, 4-IV. At month 6 (n=38), 12 (n=35) and 24 (n=20) after PEA NYHA class I/II/III/IV distribution was 28/13/4/0, 26/8/1/0 and 16/4/0/0 respectively. The mean 6-minute walk distence (6MWD) before PEA was 326 m. The mean 6MWD at 6-month, 12-monh and 24-month follow-up was 473 m, 533 m and 547 m respectively.
Conclusions. After PEA functional class according to the NYHA improved and the 6MWD increased significantly.

P06 Right ventricular remodeling after pulmonary thomboendarterectomy for chronic thromboembolic pulmonary hypertension

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Pulmonary thromboendartectomy (PTE) reduces pulmonary vascular resistance (PVR) and improves right ventricular (RV) function. N-terminal-pro-B-type natriuretic peptide (NT

proBNP) levels reflect the RV disfunction related to chronic pressure overload. Time for RV remodeling after PTE is poorly known. Objective. Assessment of the hemodynamic profile and parameters associated to RV function before and after PTE.
Methods: Hemodynamic variables during right side catheterization (PVR, right atrial pressure, cardiac output(CO)) and echocardiographic parameters of RV function (RV end diastolic diameter(RVDD), RV myocardial performance index (TEI)) and RV-LV interdependence (left ventricular eccentricity index (EI)) were obtained before and 6 months after PTE. Blood samples of NT proBNP were also obtained.
Results: 10 patients were studied (48±15 years, 7 males). There was a significatly decrease in PVR(968±386 vs 351±229 dines/cm-5) along with an improvement of CO (3.7±0.9 vs 5.9±1.9 l/min) after surgery ($p<0.05$). Echocardiographic parameters of RV morfology and function (RVDD(50±7 vs 36±4 mm), TEI(0.6±0.2 vs 0.38±0.1), EI(1.6±0.2 vs 1.0±0.1)) improved ($p<0.05$) and NT proBNP levels decreased (1922±1344vs 407±332 ng/ml, $p<0.05$) after PTE.
Conclusion: In this study, the improvement in hemodynamic predictors associated to a succesful PTE leads to a short term remodeling of RV, assessed by echocardiography and NT proBNP, a measure that is associated to RV pressure overload.

P07 Study of functional, hemodynamic and radiologic changes after pulmonary thomboendarterectomy for chronic thromboembolic pulmonary hypertension

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Pulmonary thromboendartectomy (PTE) reduces pulmonary vascular resistance (PVR) and improves functional capacity in thromboembolic pulmonary hypertension (CTEPH). Relationship between hemodynamic and radiologic findings after PTE were not yet described.
Methods: We analyzed hemodynamic parameters (PVR, right atrial pressure (RAP), cardiac output(CO)), six minute walking test (6MWT), and CT findings (mosaic parenchyma pattern score (MPP), collateral systemic circulation (CSC), pulmonary artery (PA) to aorta arterial ratio (PAR) and PA score (PAS)) before and 6 months after PTE. PAS was obtained by giving, to every affected PA, n points (x2 if completed obstruction) according to the number of branches that originate from it (max score(100%)= 40).
Results: 10 patients were studied (48±15 years, 7 males). 6MWT (345±138 vs 502±89 meters), hemodynamic paramenters (PVR(968±386 vs 351±229 dinas/cm-5), CO(3.7±0.9 vs 5.9±1.9 l/m)) and CT findings (PAR(1.3±0.2 vs 1.0±0.2) and PAS(42±18% vs 21±19%)) significantly improved ($p<0.05$) after surgery. There was not a significant change in other CT variables (CSC and MPP).
Conclusion: Hemodynamic and radiologic parameters that assess myocardial function and anatomical/func-tional characteristics of pulmonary arteries significantly improved along with functional capacity in a short time after PTE. Systemic collateral supply and parenchyma perfusion might need a longer time for recovery.

P08 Change in NT-proBNP plasma leves after after pulmonary thomboendarterectomy for chronic thromboembolic pulmonary hypertension: correlation with hemodynamic parameters

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Chronic thromboembolic pulmonary hypertension leads to an increase in pulmonary vascular resistance (PVR) which causes functional alteration of both ventricles and cardiac output (CO). Pulmonary thromboendartectomy (PTE) reduces PVR and improves right ventricular (RV) systolic function. NT proBNP is released in response to ventricular wall stretch and volume overload and correlates with prognostic hemodynamic parameters in pulmonary arterial hypertension (PAH).
Objective: To assess changes in NT proBNP levels and to compare them with modification in hemodynamic parameters after PTE.
Methods: Blood samples of NT proBNP leves and hemodynamic variables during right side catheterization (PVR, right atrial pressure, cardiac output(CO)) were obtained before and 6 months after PTE. All hemodynamic parameters were correlated to NT proBNP levels.
Results: 10 patients were studied (48±15 years, 7 males). Baseline NT proBNP levels significantly improved after PTE (1922±1344vs 407±332, $p<0.05$). PVR(968±386 vs 351±229 dinas/cm-5) and CO(3.7±0.9 vs 5.9±1.9 l/m) also improved ($p<0.05$) after surgery. Plasma NTproBNP levels significantly correlated with

CO (R=-0.8, p<0.05) and PVR (R=0.8, p<0.05) after PTE.
Conclusion: Plasma levels of NT proBNP, a measure that reflects the degree of RV overload in patients with PAH, significantly decresed after PTE and correlated with hemodynamic parameters associated to post-PTE outcome.

P09 Enhanced therapeutic strategies for support and recovery after Pulmonary Thromboendarterectomy

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Background: Pulmonary thrombo-endarterectomy (PTE) is the treatment of choice for patients with chronic thromboembolic pulmonary hypertension. However, some patients develop severe cardio-respiratory compromise soon after separating from cardiopulmonary bypass, either from early reperfusion pulmonary oedema or right ventricular failure secondary to residual pulmonary hypertension. We have used veno-arterial extracorporeal membrane oxygenation (ECMO) support in this group that has no other therapeutic option.
Methods and Materials: Retrospective review of all patients undergoing PTE from a single national referral centre between August 2005 and August 2007.
Results: 127 consecutive patients underwent PTE surgery. Seven patients (5.5%) had extreme cardio-respiratory compromise in the immediate post-operative period and required veno-arterial ECMO support. Their mean age was 51.3 years with 3 males. Mean duration of support was 119 hours (49-359 hours). Five patients were successfully weaned from ECMO support (73%) and 4 left hospital alive giving a salvage rate of 57%. For those who did not require ECMO support, hospital mortality was 4.2%.
Conclusions: Early veno-arterial ECMO support has a role as rescue therapy post PTE in patients with severe compromise who would probably otherwise die.

P10 Single center experience with 130 pulmonary endarterectomies: the impact of growing experience

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Background
Pulmonary endarterectomy (PEA) is established as a standard surgical treatment improving outcome in patients with chronic thromboembolic pulmonary hypertension. We describe our institutional experience where growing experience led to improved survival.
Methods
130 consecutive patients (66 women and 64 men, mean age 52,7 ± 14,9, range 19-80) who underwent PEA between 1993 and 2007 at our institution were retrospectively analyzed and divided in two groups : 67 patients (51%) operated between 1993-2001 (early group) and 63 patients (49%) between 2002-2007 (recent group).
Results
Patients age, circulatory arrest time and ICU stay were comparable in both groups. A highly significant postoperative improvement of the hemodynamic parameters compared to preoperative values was achieved in patients operated in both time periods. Overall perioperative mortality rate decreased from initially 12 % to recently 3,3 %. 1 year survival increased from 85,1 % (1993-2001) to 95,1% (2002 -2007). The causes of death were right ventricular failure (n=6) and bleeding (n=1) in the early group and right ventricular failure (n=2) and sepsis (n=1) in the recent group.
Conclusion
We conclude that growing experience and better management of perioperative complications leads to significantly improved survival after PEA.

P11 Intermittent Circulatory Arrest under Cerebral Near-Infrared Spectroscopy (NIRS) Monitoring to Improve Cerebral Protection during Pulmonary Endarterectomy

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Purpose: Pulmonary endarterectomy (PEA) has been accepted as the treatment of choice for chronic thromboembolic pulmonary hypertension. To achieve complete PEA

circulatory arrest is required. Best strategy for cerebral protection is still debated. We present our experience using intermittent circulatory arrest under NIRS monitoring.
Methods: Over 14-year period 185 PEAs were performed. Strategy of cerebral protection has changed during study period. Lately intermittent periods of circulatory arrest (10 minutes) followed by 5-minute periods of reperfusion has been our procedure of choice. NIRS monitoring has been lately used in order to optimize the duration of arrest and reperfusion periods. Postoperative outcomes of patients undergoing NIRS monitoring were compared to those not receiving NIRS monitoring.
Results: Sixty-five pts received NIRS monitoring during PEA. Mean periods of circulatory arrest (4.2±2.2 vs. 2.1±1.5) and minutes of total circulatory arrest (55±26 vs. 33±24) were significantly higher in patients with NIRS monitoring. Moderate vs. deep hypothermia was used significantly more in patients receiving NIRS monitoring (16 vs. 6 %). Despite prolonged total circulatory arrest and moderate hypothermia, patients receiving NIRS monitoring presented similar incidence of transient neurological complications (13 vs. 12 %).
Conclusions: NIRS monitoring allow for satisfactory cerebral protection even in moderate hypothermia. Such technique seems to safely allow prolonged total circulatory arrest to achieve complete endarterectomy.

P12 Long-term Hemodynamic and Functional Results After Pulmonary Endarterectomy

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Purpose: Early results following pulmonary endarterectomy (PEA) are known to be excellent. Currently, however, long-term data are lacking.
Methods: We analyzed data obtained from 185 consecutive PEAs performed at our Center from April 1994 to April 2008. Patients were studied preoperatively, at discharge, at 3 months and 1, 3, 5, 7, and 10 years post-operatively. We assessed right heart hemodynamics by catheterization, right ventricular (RV) function and geometry by echocardiography, lung function by standardized PaO2, and functional status by modified Bruce test and NYHA class evaluation. Survival curve was calculated.
Results: Operative mortality was 10.3% (19/185). Hemodynamics dramatically improved within a few post-operative days. RV geometry and lung function almost normalized within a few weeks from surgery. Exercise tolerance required almost 1 year to fully recover. RV function and functional capacity steadily improved over time. Cumulative survival was 88% at 3 months, 87% at 1 year, 84% at 3 and 5 years, and 80% at 7 and 10 years postoperatively.
Conclusions: PEA is a highly effective procedure. Hemodynamic, respiratory, and functional results are proved to be durable over time until 10 years after EAP. Mortality rate after the first postoperative year is comparable with that of the age-matched general population.

P13 Endothelial Cell-specific deletion of VEGF-R2/flk-1 results in a failure of thrombus resolution

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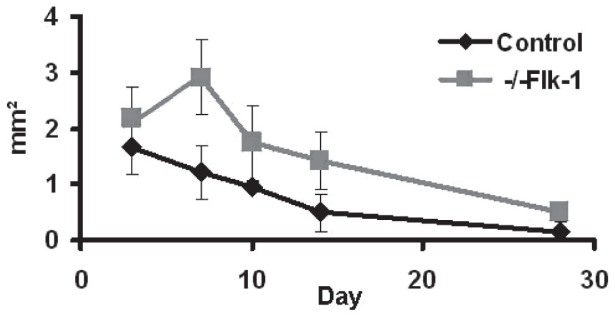
Background: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by occlusive vascular remodeling of pulmonary thromboemboli. The mechanisms underlying misguided thrombus resolution in CTEPH are still unclear. Previous studies have demonstrated an involvement of angiogenic molecules in the pathogenesis of pulmonary hypertension. To test the role of angiogenesis in thrombus resolution, we investigated the effect of an endothelial cell-specific deletion of VEGF-R2/flk-1, an important regulator of angiogenesis, in a murine model of stagnant flow venous thrombosis.
Methods: Thrombosis was induced in the infrarenal vena cava of Tie2/Cre flk-1 flox/flox mice on a C57/BL6 background by creating a venous stenosis with a silk suture. Thrombi were harvested on days 3, 7, 10, 14 and 28 after surgery (n=8 per time point). Non-transgenic siblings served as controls.
Results: Thrombus cross-sectional area analysis over time demonstrated a significant increase in thrombus area by day 7 after surgery in flk-1-/- animals compared with controls (ANOVA, $p<0.05$) (Figure 1).
Conclusion: Cell-specific deletion of VEGF-R2/flk-1 leads to misguided thrombus resolution. The data demonstrate that angiogenesis plays a crucial role in thrombus resolution.



P14 Chronic Thromboembolic Pulmonary Hypertension (CTEPH) and associated medical conditions

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Objective: CTEPH is characterized by nonresolving pulmonary thromboemboli. Although traditional thrombosis risk factors are absent, CTEPH-predisposing medical conditions, such as splenectomy, ventriculo-atrial (VA-) shunts and certain inflammatory disorders have been identified. We sought to confirm CTEPH risk factors in a large cohort of prevalent CTEPH cases collected in 3 European centers offering pulmonary endarterectomy.
Methods: Data were compared with pulmonary arterial hypertension cohorts (Table 1).
Results: The study population comprised 538 patients (pts) assessed at the time of diagnosis between 1992 and March 2007. Among 389 pts with CTEPH were 53% females, mean age 56±14 years and a pulmonary vascular resistance of 827 (574-1102) dynes.s.cm-5.
Conclusions: The data confirm that anti-phospholipid antibodies (APA), splenectomy and VA-shunts are CTEPH risk factors. In addition, thyroid replacement therapy, malignancy and previous venous thromboembolism (VTE) are associated with CTEPH. The data indicate that CTEPH pathogenesis is complex and involves factors beyond traditional thrombosis.

Medical conditions and adjusted odds ratios for the risk of CTEPH (partial effects)

Condition	Odds Ratio (95% CI)	P-value
thyroid replacement	4.80 (2.11-12.02)	<0.01
malignancy	3.41 (1.24-10.89)	0.02
previous VTE	19.27 (10.60-37.52)	<0.01
infected leg ulcers	2.86 (0.97-10.09)	0.06
APA	3.09 (1.15-9.22)	0.02
SLE	0.12 (0.00-1.13)	0.07
VA-shunt	37.01 (3.47-5104)	<0.01
splenectomy	10.90 (1.17-1466)	0.03

P15 Splenectomy is associated with misguided thrombus resolution

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Purpose: Splenectomy is associated with an increased risk of chronic thromboembolic pulmonary hypertension (CTEPH). CTEPH is a life-threatening condition characterized by single or recurrent pulmonary thromboemboli that obstruct or obliterate the pulmonary vascular bed. The aim of our study was to investigate pathomechanisms of altered thrombus formation and resolution after splenectomy.
Methods: We utilized a mouse model of stagnant flow venous thrombosis to characterize venous thrombus formation and resolution. Vena cava ligation was performed one month after splenectomy. At days 3, 7, 14 and 28 after vena cava ligation thrombi were harvested for histology and mass spectrometry analysis. Blood samples were collected for FACS.
Results: Thrombus areas of splenectomized mice were significantly larger than those of controls at all time points (ANOVA, n=8, p<0.03). Whole blood FACS revealed a higher counts of CD41-platelet microparticles (day 14: 3216 versus 927 cells/µl, p< 0,05) and leukocyte/platelet aggregates (day 14: CD11b/CD41, 56,4 versus 38,7%, p<0.05). In parallel, negatively charged phospholipids were 10 - fold increased in thrombi of splenectomized mice by day 14.
Conclusion: Splenectomy delays thrombus resolution in a pattern that is strikingly different from thrombus resolution observed in sham-operated animals. The loss of mechanical filtering by the spleen permitting the accumulation of anionic phospholipids in the peripheral circulation is a key mechanism of thrombus persistence.

P16 Prevalence of pulmonary hypertension in patients after splenectomy

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Background. Patients after splenectomy are at increased risk of developing chronic thromboembolic pulmonary hypertension (CTEPH). However, the prevalence of CTEPH among splenectomized individuals is unknown.

Methods. In the context of the pulmonary hypertension (PH) screening program at the Medical University of Vienna, 1100 general practitioners and internal medicine specialists in Vienna and Lower Austria were invited to refer patients (pts) at least one year after splenectomy. Screening was performed by transthoracic echocardiography with Doppler. In cases of elevated systolic pulmonary arterial pressure (sPAP>40mmHg) and absence of left ventricular or valvular dysfunction, right heart catheterization was performed.
Results. Between November 2006 and October 2007, 91 pts were referred (50males/41 females). Mean age was 52.6±14.2 years. Median time since splenectomy was 143 months. Reasons for splenectomy were trauma (n=39), hematological disorders (n=18), surgical complications (n=18) and others (n=16). CTEPH was newly diagnosed in 4 pts who had suffered from exertional dyspnea.
Conclusion. CTEPH was diagnosed in 4.4% of pts after splenectomy. Echocardiographic screening for CTEPH is useful after splenectomy, especially in pts with unexplained dyspnea.

P17 Electrocardiography and serum N-terminal brain natriuretic peptide for diagnostic decision making in pulmonary hypertension

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Background. Current diagnosis guidelines for precapillary pulmonary hypertension (PH) recommend right heart catheterization (RHC) in patients with echocardiographic systolic pulmonary pressures (sPAP) ≥36mmHg. The growing awareness for PH, a high prevalence of postcapillary PH and the inability to discern between pre- and postcapillary PH by transthoracic echocardiography (TTE), have led to an excessive amount of RHCs in unaffected individuals. The aim of the present study was to test the ability of 12-lead electrocardiography (ECG) to discriminate between pre- and postcapillary PH in a pre-selected patient population with clinical and TTE suspicion of PH.
Methods. At a high-volume tertiary referral center for PH, admission ECGs of 251 patients were retrospectively analyzed by two cardiologists blinded to the TTE and hemodynamic parameters. We evaluated the diagnostic value of clinical parameters, N-terminal brain natriuretic peptide (NT-proBNP) and ECG findings compatible with precapillary PH. Based on parameters with the highest discriminative abilities as derived from logistic regression, we constructed decision trees and performed receiver operating characteristics (ROC) analyses.
Results. NT-proBNP (OR[95%CI] 2.01[1.21-3.33], p=0.007) and right ventricular strain (RVS) on ECG (OR[95%CI] 52.91[17.27-162.10], p<0.001) were independent predictors of precapillary PH and were automatically selected for decision tree construction. ROC analysis of the tree-based algorithm yielded incremental diagnostic information as compared to the currently used sPAP on TTE (area under the curve 0.925 vs. 0.849).
Conclusion. The incorporation of ECG and NT-proBNP into diagnostic decision making with respect to RHC may add significant independent predictive power to the current use of TTE alone.

P18 Structural changes of the pulmonary vasculature in patients with chronic thromboembolic pulmonary hypertension

W. Yao, R.S. Sacks, A. Ogawa, A.L. Firth, W.R. Auger, M. Madani, N. Sakakibara, P.A. Thistlethwaite, S.W. Jamieson, L.J. Rubin, J.X.-J.Yuan
(University of California, San Diego, Department of Medicine)

Chronic thromboembolic pulmonary hypertension (CTEPH) is resultant of a single or recurrent pulmonary thromoemboli arising from sites of deep venous thrombosis that are not resolved by conventional anti-coagulant therapy. The mechanism for the poor resolution of the initial thromboembolismremains to be elucidated. The persistent thrombus tightly attaches to the pulmonary arterial medial layer, replacing the normal intima and occludes the central pulmonary artery preventing blood flow to more distal lung regions, resulting in the elevated pulmonary vascular resistance (PVR), causing right heart failure and ultimately, without therapeutic intervention, death. Pulmonary endarterectomy (PTE) is currently the treatment of choice for CTEPH patients with unresolved thromboemboli (figure shown below). The pathogenesis of CTEPH is still unclear.
Tissue collection and cell isolation
Endarterectomized tissues were obtained directly from operating room after pulmonary endarterectomy(PTE) and preserved in cold phosphate-buffered saline (PBS) for transport to the lab for histological preparation and cell

isolation. All the protocols were approved by the Institutional Review Board of University of California, San Diego.
ImmunohistochemistryTissue sections prepared from endarterecomized tissues were stained with α-SM-actin antibody and CD45 antibody, respectively. Secondary antibodies goat-anti mouse IgG-HRP and goat anti-rat IgG-HRP were then used. Signal was visualized by ABC methods.
ImmunofluorescenceTissue sections and isolated cells were stained with CD34, Flk-1, pro-collagen1 anitodies, respectively, and then stained with goat anti-mouse IgG-FITC, bovine anti-rabbit IgG-TRITC. The samples were counter stained with DAPI. RT-PCRmRNA isolated from normal PASMCs, hPAEC, and CTEPH cells were reverse transcribed to cDNA. GAPDH, CD34, Flk-1, and CD133 were amplified. Flow cytometryCTEPH cells and normal hPASMCs were triple stained with CD34-PE, Flk-1-FITC, and CD133-APC and quantified with a flow cytometer.
The obstruction in the pulmonary arteries of CTEPH patient is a recanalized fibromuscular structure. mouse IgG-HRP and goat anti-rat IgG-HRP were then used. Signal was visualized CD34/Flk-1/DAPI Endothelial progenitor cells (CD34+/Flk-1+/CD133+) are present in endarterectomized tissues from CTEPH patients. Endothelial progenitor cells, originated from bone marrow, may play a role in the development of the vascular occlusion, recanalization, and vascular remodeling.
Circulating progenitor cells, trapped in the thromboemboli, may use the stabilized thromboemboli as a „niche" to become abnormal or misguided progenitors involved in the development of CTEPH.

P19 Vast morphological diversity exists in cells isolated from endarterectomized tissue from patients with chronic thromboembolic pulmonary hypertension

A. L. Firth, A. Ogawa, W. Yao, O. Platoshyn, C.V. Remillard, R.S. Sacks,W.R. Auger, M. Madani, P.A. Thistlethwaite, S.W. Jamieson, J.X.-J. Yuan
(University of California, San Diego, Department of Medicine)

Chronic thromboembolic pulmonary hypertension (CTEPH) is a relatively common and very serious complication of acute pulmonary embolism. It isestimated that up to 4% of patients with acute pulmonary embolism develop CTEPH; however the prevalence and incidence of CTEPH is deemed to be grossly underestimated. Despite having well defined clinical directives, the pathogenic mechanisms involved in CTEPH are currently unknown.
This study was designed to characterize the morphological heterogeneity in cell populations isolated from excised pulmonary endarterectomy (PTE) tissues using phase contrast, immunofluorescenceand molecular biological techniques.
Cells were isolated from surgically removed pulmonary vascular tissues from patients with CTEPH undergoing pulmonary endarterectomy after written informed consent was acquired. Protocols were approved by the IRB of UCSD. Isolated cells were grown in smooth muscle growth media and used for experiments as primary cells and at passages 2-6.
Primary antibodies and secondary antibodies conjugated to PE, FITC and Rhodaminewere used. Imgeswere taken at 20x magnification using a deconvolution microscope and DeltaVisionsoftware package SoftWorx(version 2.50). RNA was extracted from cells and cDNA synthesized with SuperScript II reverse transcriptase. RT-PCR was performed using Platinum Blue PCR Supermix. The sequences of the primers were specifically designed from the coding regions of the selected genes.
Diverse morphological heterogeneity was observed in cultures of cells isolated from PTE tissues. Cells expressed SMαA differentially; some having strong filaments organization, others general cytoplasmic expression and some with expression. A variety of markers typical of immature cells were expressed, most prominently SMαA, Nestin, Vimentin and CD117 (C-Kit). mRNA of markers typical of Mesenchymal progenitor cells were strongly expressed; CD-29,CD-73 and CD-90. Myofibroblasts were a prominent cell type staining strongly for Vimentin and expressing different levels of SMαA. CD-105 positive cells were present with smaller more immature cell types expressing CD-105 strongly. Populations of cells positive for STRO-1 and CD-73 were also present. Cellular co-localization of CD-105 and CD-73 and STRO-1 and CD-73 was observed.
A morphologically diverse population of cells is present in cell populations isolated from PTE tissues. The majority of cells were of an immature cell types and included a defined population of mesenchymal progenitor type cells. The specific microenvironment or „niche" in the pulmonary arteries of CTEPH patients may attract or stimulate abnormal growth and differentiation of these cells leading to the poor resolution of the fibrotic embolism in these patients.

Saturday, June 7, 2008

CLINICAL SCIENCE

Epidemiology and risk factors
9.00 – 10.30

19 Predictors for fatal pulmonary embolism

D. Jiménez
(Ramón y Cajal Hospital, Department of Medicine, Respiratory Department)

Although most patients with acute pulmonary embolism (PE) have an uncomplicated clinical course while undergoing standard anticoagulation treatment, the overall 3-month mortality rate exceeds 15%. Death from acute PE usually occurs before or soon after hospital admission. Patients presenting with clear signs of shock have high morbidity and mortality rates. It is generally accepted that these patients should be considered for thrombolytic therapy. One area of controversy focuses on the extension of the indication for thrombolytic therapy to a subgroup of patients who appear stable at presentation but have impending right ventricular failure and high risk of PE-related death. Thus, a major challenge is the identification of such potential candidates for thrombolytic therapy by a simple, rapid and non-invasive method.
Using data from the international prospective Registro Informatizado de la Enfermedad TromboEmbolica venosa (RIETE) registry, we determined independent predictive factors for fatal PE (1). On multivariable analysis, clinical factors independently associated with an increased risk of fatal PE were symptomatic nonmassive PE (5.42-fold higher) (compared to patients with deep vein thrombosis at presentation), symptomatic massive PE (17.5-fold higher), immobilization for neurological disease (4.90-fold higher), age > 75 years (2.54-fold higher), and cancer (2.04-fold higher).
This presentation will also discuss the prognostic value of right ventricular dysfunction (assessed by transthoracic echocardiography or elevated serum troponin levels) (2, 3) and thrombus burden (estimated by lower limb ultrasound testing), alone or in combination, for identifying hemodynamically stable patients whom may benefit from thrombolytic treatment.

20 Chronic Thromboembolic Pulmonary Hypertension (CTPH): a common consequence of acute Pulmonary Embolism (PE)?

V. Pengo
(Clinical Cardiology, Thrombosis Centre, University of Padua, Italy)

Chronic pulmonary hypertension is considered a relatively rare complication of pulmonary embolism but is associated with considerable morbidity and mortality. It is commonly believed that symptoms become manifest only several years after the initial episode of pulmonary embolism. However, the true frequency of CTPH after an acute PE is not well established, It was estimated at 0.1 percent in early '90s, at 0.5 percent in early 2000 but some Authors reported an incidence as high as 5.1%. In our recent study on 227 first episodes of PE, the cumulative incidence of symptomatic CTPH was 1.0 percent at six months, 3.1 percent at one year, and 3.8 percent at two years. Discrepancies between these results might be explained with underdiagnosis of PE especially in young people and during pregnancy and puerperium, asymptomatic episodes of PE, selection bias, different definitions of CTPH. Clinical suspicion and an accurate diagnosis of PE and diagnosis of recurrent events could avoid the development of CTPH.

21 Novel risk factors for CTEPH

D. Bonderman
(Medical University of Vienna, Department of Internal Medicine II)

Aims: Chronic thromboembolic pulmonary hypertension (CTEPH) is characterized by non-resolving pulmonary thromboemboli that can be treated by surgical pulmonary endarterectomy (PEA). We sought to confirm known and to identify novel CTEPH risk factors in controlled retrospective cohort study of prevalent CTEPH cases collected in 3 European centers offering PEA.
Methods and Results: Data from CTEPH patients were compared with non-thromboembolic pulmonary arterial hypertension cohorts at the participating institutions. The study population comprised 687 patients assessed at the time of diagnosis between 1996 and 2007. VA-shunts and infected pacemakers (odds ratio (OR) and 95% confidence interval, 76.40 [7.67-10351], p<0.001), splenectomy (OR 17.87 [1.56-2438], p=0.017), previous venous thromboembolism (VTE) (OR 4.52 [2.35-9.12], p<0.001), recurrent VTE (OR 14.49 [5.40-

43.08], p<0.001), blood groups non-0 (OR (OR 2.09 [1.12-3.94], p=0.019), and lupus anticoagulant/anti-phospholipid antibodies (OR 4.20 [1.56-12.21], p=0.004) were more often associated with CTEPH. Thyroid replacement therapy (OR 6.10 [2.73-15.05], p<0.001) and a history of malignancy (OR 3.76 [1.47-10.43], p=0.005) emerged as novel CTEPH risk factors. Conclusions: This European database confirmed previous knowledge on CTEPH risk factors, and identified thyroid replacement therapy and a history of malignancy as new medical conditions associated with CTEPH.

22 Incidence of CTEPH in the UK
J. Pepke-Zaba
(Papworth Hospital, Pulmonary Vascular Diseases Unit, Cambridge, UK)

Not available as per date of printing

Pulmonary vasculature in CTEPH

11.00 – 12.30

23 Development of the bronchial circulation
M.K. Renner
(Department of Cardiology, Medical University Vienna
Results: Thrombus areas of splenectomized mice were significantly larger than those of controls at all time points (ANOVA, n=8, p<0.03). Whole blood FACS revealed a higher counts of CD41-platelet microp)

From the earliest stage of lung development, the vascular units are in close coordination with airways and alveoli. While many of the genes initiating lung morphogenesis, the determination of left-right asymmetry and laterality, and the regulation of airway branching have been identified, less is known about genes regulating vascularization. During early fetal development, the airways act as a template for pulmonary blood vessel development in which the vessels form by vasculogenesis around the branching airways. In later lung development, as the alveoli multiply, new capillaries form by angiogenesis, the latter including sprout formation, splitting or intususceptive (i.e. of-itself) microvascular growth, and simple expansion. By the addition of mural cells, they develop a muscle wall that is relatively thick during fetal life and shows a rapid reduction after birth. As vascular networks increase in size and three-dimensional complexity, growth is accompanied by regression of unneeded units until these are appropriate to the stage of lung development. In this way, vascular systems formed in utero develop, enlarge and are remodeled until thoracic growth is complete. Pulmonary vascular tone is regulated by a complex, interactive group of mechanisms during fetal life and the transition to extra-uterine air breathing. PGI2, leukotrienes, NO and NO-mediated mechanisms are vasoactive factors involved in the regulation of pulmonary vascular resistance and in the perinatal transition process. Abnormal pulmonary vascular development leading to pulmonary arterial hypertension, for example caused by dysfunctional bone morphogenetic protein (BMP) - signalling and strategies for treatment are currently interests of research.

24 Evaluation of pulmonary vascular disease in CTEPH
N.H. Kim
(University of California, San Diego)

Chronic thromboembolic pulmonary hypertension represents a two-compartment disease: major vessel, proximal obstructive defect that is surgically treatable, and varying degrees of small-vessel disease with histopathologic features similar to idiopathic pulmonary arterial hypertension. Our current diagnostic tools primarily focus on the presence or absence of proximal disease. As the major contributor to post-endarterectomy morbidity and mortality relates to the presence of significant, concomitant small-vessel disease, we need better means of preoperatively identifying this high risk sub-population of CTEPH patients. This session overviews current and emerging preoperative tests employed in the evaluation of CTEPH.

25 Differential Diagnosis of CTEPH - Physician's view
H. Wilkens
(Universitätskliniken Homburg, Germany)

CTEPH a frequent cause of pulmonary hypertension, however it is commonly underdiagnosed. It is important to differentiate CTEPH from other forms of pulmonary hypertension (PH) to target treatment, since the therapeutic approach to CTEPH can differ substantially from that to PAH. Symptoms are nonspecific, patients present with progressive dyspnea on exertion, rapid exhaustion and other signs of right heart insufficiency. These symptoms can be indistinguishable from other forms of severe pulmonary hypertension, since there is no known history of thromboembolic

disease in more than 50% of cases. Echocardiography is mostly used as the initial screening investigation to identify patients with suspected pulmonary hypertension. A ventilation-perfusion scintigram is a useful tool to search for possible CTEPH, a normal ventilation-perfusion scan makes the diagnosis of CTEPH very unlikely. The presence of bilateral mismatched segmental defects is suggestive of the diagnosis, however, other diseases including pulmonary veno-occlusive disease, pulmonary capillary hemangiomatosis, pulmonary vasculitis, sarcomas of the pulmonary arteries or fibrosing mediastinitis may cause similar findings. When CTEPH is suspected multislice computed tomography CT distinguishes CTEPH from idiopathic arterial PH, evaluates underlying lung disease, and may help to identify rarer causes of PH. It has to be kept in mind, however, that in patients with PAH extensive in situ central pulmonary artery thrombosis may rarely be mistaken for CTEPH, and in patients with sarcoma of the pulmonary arteries or with pulmonary arteritis similar findings can be obtained. MRI also provides a diagnosis of CTEPH, gives information about right ventricular function and may be useful in discriminating central thromboembolic lesions from tumors. Complete embolic occlusion of a pulmonary artery may be difficult to dicriminate from unilateral agenesia of the pulmonary artery. The diagnosis of CTEPH is based on a stepwise use of immaging tools, in patients for whom pulmonary endarterectpmy could be a therapeutic option pulmonary angiography is finally performed to confirm the diagnosis and to assess the operability and is performed in conjunction with a right heart catheterization.
The diagnosis and management of chronic thromboembolic pulmonary hypertension requires a multidisciplinary approach.

26 Differential Diagnosis of CTEPH - Surgeon's view

W. Klepetko
(Department of Cardiothoracic Surgery, Medical University of Vienna, Austria)

CTEPH usually presents with a typical clinical and angiographic picture which allows to establish the correct diagnosis. However, there are several other diseases which might mimick similar circumstances like CTEPH and it is of crucial importance to diagnose these diseases preoperatively. Of special importance are angiosarcomas which can occure in about 2 – 3 percent of patients. Rapid intravascular growing of a lesion, together with unilateral occurence are suggestive for this entity.
However, unilateral total occlusion of an pulmonary artery occurs in about 8 to 10 percent of patients and can as well be a typical CTEPH manifestation.
Other possibilities in the differential diagnosis are connective tissue diseases such as Takayashu-syndrom of the PA which can be seen on rare occasions.
Of highest importance certainly is the differentiation between very distal forms of CTEPH and in situ thrombosis superimposed to PPH or other forms of Eisenmenger Disease.
Careful evaluation of patient history, together with angiographic and CT based workup allows to establish the correct diagnosis in the majority of cases. However there remains a certain small percentage of patients, where the final diagnosis can be established only intraoperatively.

Interactive Case Session
13.30 – 15.30

27 Case 1 - Case of unilateral perfusion defect

N. Kim
(University of California, San Diego)

Question 1: Which of the following is the most common cause of this VQ scan?
Choices:
a) Mediastinal fibrosis
b) Large vessel vasculitis
c) Pulmonary artery sarcoma
d) Chronic thromboembolic disease

Question 2: Which of the following tests would you order next?
Choices:
a) CT angiogram
b) Pulmonary arteriogram
c) MRA
d) Right heart catheterization

Question 3: Which would you NOT expect in association with this disease?
Choices:
a) Normal PAP
b) No symptoms
c) Poor prognosis
d) No improvement with thrombolytic

Question 4: Which is the current recommended first line treatment?
Choices:
a) Surgery
b) Anticoagulation for 3 months
c) Chemotherapy
d) Radiation therapy

28 Case 2 - Is this CTEPH?
M. Delcroix
(Universitaire Ziekenhuizen Leuven)

This is the case of a 62 y old lady, with a history of alcoholism and liver cirrhosis. In 2005 she had an episode of right heart failure. Since 2002, she complains of progressive shortness of breath (NYHA class III). At the end of 2007, she had an echoDoppler examination of the heart showing severe pulmonary hypertension and an angioCT of the thorax showing massive thrombi in both pulmonary arteries. She was treated with oral anticoagulans but did not improve significantly. She was explored in a reference center. A right heart catheterisation showed severe pulmonary hypertension with a low cardiac index. AngioCT was unchanged but the perfusion scan of the lungs was normal.

29 Case 3
J. Pepke-Zaba
(Papworth Hospital, Pulmonary Vascular Diseases Unit, Cambridge, UK)

Not available as per date of printing

30 Case 4 - Pulmonary Artery Thrombosis and Pulmonary Embolism in a Patient with Eisenmenger Syndrome
S. Mebus
(German Heart Centre Munich, Paediatric Cardiology and Congenital Heart Defects)

A 32-year-old man with Eisenmenger Syndrome caused by ventricular inversion (ccTGA) with non-restrictive, large ventricular septal defect (VSD) was admitted to our hospital. At the age of 1 year, he underwent an operation with pulmonary arterial banding and Blalock-Hanlon atrioseptectomie. Unfortunately the pulmonary arterial banding was ineffective and the patient developed a severe pulmonary vascular disease with pulmonary hypertension and Eisenmenger Syndrome.
For several years he had been classified as functional class II. His oxygen saturation was about 87%, haemoglobin was about 18 mg/dl. Echocardiography visualized a mild tricuspid regurgitation with a systemic pressure in the right ventricle and the pulmonary arteries. Because of previous histories of atrial and ventricular arrhythmias in the past, the patient got an electrophysiology study, miscellaneous antiarrhythmic drugs and Aspirin was prescribed. Mentionably the patient smoked cigarettes regularly.
Due to a relocation the patient missed any further cardiological follow-ups in-between 2002 and 2007. In January 2007 he was hospitalised for clinical worsening with a common cold and episodes of haemoptysis, which occurred since some months before presentation. On admission, the patient had been classified as functional class III. Oxygen saturation was about 77%, haemoglobin was about 21 mg/dl. Blood samples revealed a slightly elevated C-reactive protein level, but normal white blood cell count. Platelet count was normal, while D-dimers were markedly elevated. Echocardiography and chest x-ray showed massive dilated pulmonary arteries, confirmed by computed tomography and cardiac MRI, which in addition revealed circumferential mural thrombosis. Furthermore, bilaterally pulmonary embolism and inflammatoric pulmonary infiltrations were detected.
Phenprocoumon treatment with a target value of international normalized ratio 2,0 to 2,5 was initiated. Haempotysis stopped and no bleeding complications occured until now. Because the patient did not recover to his previous functional status, bosentan treatment was started. So far, the patient is in a clinically steady state without any new thromboembolic or bleeding complications.

31 Case 5
H. Wilkens
(Universitätskliniken Homburg, Germany)

Not available as per date of printing

32 Case 6
J.L. Vachiéry
(ULB Hopital Erasme, Pulmonary Hypertension Clinic Cardiology, Brussels, Belgium)

Not available as per date of printing

33 Case 7
R. Sadushi-Kolici
(Medical University of Vienna, Department of Internal Medicine II)

Not available as per date of printing

Treatment of CTEPH
15.30 – 17.00

34 Suitabilty for PEA – the Czech Experience
J. Lindner
(General University Hospital, II Internal Clinic)

Not available as per date of printing

35 Surgical Techniques to treat CTEPH
E. Mayer
(Department of Thoracic Surgery, Catholic Academic Hospital Mainz, Germany)

Chronic thromboembolic pulmonary hypertension (CTEPH) is one of the leading causes of severe pulmonary hypertension. Although the diagnosis can be easily suspected by echocardiography and lung perfusion scanning, CTEPH is an under-recognized and frequently overlooked condition with a poor prognosis. Pulmonary endarterectomy (PEA) is an effective surgical procedure providing an acute and permanent relief of thromboembolic pulmonary hypertension and potential cure for most of the patients.
Based on high quality pulmonary angiograms, operability and indication for surgery have to be evaluated by an interdisciplinary team including an experienced surgeon for each individual patient. Pulmonary endarterectomy is a complex procedure: It resembles a true endarterectomy (not embolectomy) of the pulmonary artery branches down to the segmental and subsegmental levels. Extracorporeal circulation and periods of hypothermic circulatory arrest are mandatory. In specialized centres, the operative risk has been decreased to acceptable levels (<10 %). Long-term survival and quality of life are excellent after successful surgery even in patients with end-stage thromboembolic pulmonary hypertension and right heart failure. Although CTEPH is primarily considered a major-vessel disease, secondary microvasculopathy develops in unaffected pulmonary artery branches over time. Therefore, earlier diagnosis and referral for surgery might further improve early and late results by reducing the severity of small vessel disease. As the procedure is complex, patients should be treated by a specialized multidisciplinary team.

36 Summary of targeted treatment trials in CTEPH and subgroup analyses
N. Galie
(Institute of Cardiology, University of Bologna, Italy)

Not available as per date of printing

37 Impact of the BENEFIT trial- which end-points might be best for clinical trials of future medical therapies in CTEPH?
A. Torbicki
(Institute of Tuberc. Lung Dis., Warsaw, Poland)

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