509. Clinical features of human pulmonary hypertension

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Late-breaking abstract: Demographic trends and changes In long term outcome of *incident* idiopathic, heritable and anorexigen-associated pulmonary arterial hypertension between 2001 to 2009. Results from the Pulmonary Hypertension Registry of the United Kingdom and Ireland

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Background: There have been significant changes in the management of pulmonary arterial hypertension (PAH) over the past decade. In the UK and Ireland, care of pulmonary hypertension (PH) is centralised to designated PH centres. This provides an excellent opportunity to study changes in demographic and survival trends of the disease within an entire region with a common healthcare system.
Aim: To determine whether baseline characteristics and survival of *incident* IPAH, heritable and anorexigen-associated PAH has changed over the past decade.
Methods: Retrospective observational study of all *incident* cases of IPAH, heritable and anorexigen-associated PAH diagnosed in the UK and Ireland between 1st January 2001 and 31st December 2009.
Results: Total of 646 patients were diagnosed (22% in 2001-2003, 33% in 2004-2006 and 45% in 2007-2009). In recent years, patients were older, had higher BMI, lower % predicted diffusion capacity for carbon monoxide (DLCO) and had more co-morbidities (COPD, ischaemic heart disease and diabetes). There is no difference in unadjusted overall survival from 2001 to 2009. However, after adjusting for age, % DLCO, 6 minute walk distance and cardiac index, patients diagnosed in the 2001-2003 period were likely to have a shorter survival time compared to those diagnosed in 2007-2009 (hazard ratio 1.7, 95% CI 1.1-2.6)
Conclusion: After adjusting for potential confounders, survival of *incident* IPAH, heritable and anorexigen-associated PAH in the UK and Ireland has improved over the last decade.

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Right ventricular (RV) remodelling in PAH: Impact of RV mass/volume ratio on survival

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Pulmonary arterial hypertension (PAH) is characterized by an impressive increase in pulmonary vascular resistances (PVR) that causes severe right ventricular (RV) dysfunction. Because the pathophysiologic model is an afterload mismatch we hypotisize that the best RV adaptation is a concentric hypertrophy (high RV mass/volume ratio (RV M/V)).
Methods: 63 consecutive patients with PAH (50 idiopathic, 13 associated to SSc) who underwent clinical (NYHA class) effort capacity (6MWT, six-minute walk-test) hemodynamic and heart magnetic resonance evaluation as routine work-up at the time of diagnosis. Population was divided in two groups on the basis of median value of RV M/V (cut-off 0,6) and followed-up for deaths (average 2.3 years).
Results: Patients with RV M/V>0.6 have lower RV systolic and diastolic volumes but similar RV mass compared to patients with RV M/V<0,6. Despite no significant differences in clinical status, effort capacity and hemodynamics between the two groups, patients with RV M/V>0,6 have a lower mortality compared to patients with RV M/V<0,6.

	RV M/V < 0,6 n=32	RV M/V > 0,6 n=31	p<
Age	50±16	54±14	0,05
NYHA	2,4±0,6	2,3±0,6	ns
6MWT,m	412±122	426±118	ns
RV EDV, ml	172±65	131±32	0,002
RV ESV, ml	116±64	86±31	0,02
RV EF, %	35±14	35±12	ns
RV mass	78±29	91±23	0,04
Pra, mmHg	7±3	7±4	ns
Ppa, mmHg	53±19	52±16	ns
CI, l/m'/m^2	2,3±0,8	2,3±0,7	ns
PVR, WU	12±9	12±9	ns
Death, n	7/32	1/31	0,007

EDV = end-diastolic volume; ESV = end-systolic volume.

Conclusion: In PAH it is possible to identify a subgroup of patients with RV hypertrophy and moderate diastolic volume increase (i.e. high RV mass/volume ratio) which has a low rate of deaths, suggesting a better RV adaptation to the increased afterload.

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Pulmonary arterial hypertension in patients with chronic kidney disease on dialysis and without dialysis: Results of the PEPPER-study

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Background: Pulmonary hypertension (PH) is common in patients with dialysis-dependent chronic kidney disease (CKD) and is an independent predictor of mortality. However, specific hemodynamics of the pulmonary circulation, changes induced by hemodialysis and prevalence of pulmonary arterial hypertension (PAH) have not been evaluated in patients with CKD.
Methods and results: We assessed consecutive patients with CKD on hemodialysis (group 1, n=31) or without dialysis (group 2, n=31), in World Health Organization functional class ≥II with dyspnea unexplained by other causes, using right heart catheterization (RHC). In group 1 RHC was performed before and after dialysis. PAH was diagnosed if mean pulmonary arterial pressure (mPAP) was ≥25 mmHg and pulmonary capillary wedge pressure (PCWP) ≤15 mmHg (after dialysis in group 1) and if other causes of PH were excluded. In CKD patients after dialysis, prevalence of PH was 24/31 (77%; 20/31 postcapillary PH, 4/31 precapillary PH); prevalence of PAH was 3/31 (10%). After dialysis, there were significant decreases in mPAP and PCWP; all four cases of precapillary PH were unmasked by dialysis. In group 2, postcapillary PH was diagnosed in 22 cases (71%); no cases of PAH were detected.
Conclusions: The finding that the prevalence of PAH was 10% in CKD patients on hemodialysis who have unexplained dyspnea suggests careful screening for PH in this patient population is warranted. The possibility that dialysis might be a trigger for the development of PAH is plausible given that there were no instances of PAH in the nondialysis CKD patient group. RHC should be performed after dialysis to unmask precapillary PH.

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Left atrial volume to distinguish idiopathic pulmonary arterial hypertension from pulmonary hypertension due to left heart disease

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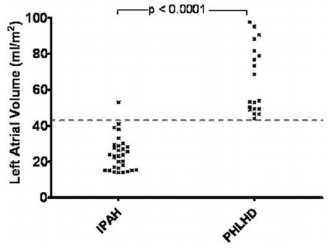
Introduction: It can be difficult to distinguish pulmonary arterial hypertension (which will respond to disease targeted therapy) from pulmonary hypertension due to left heart disease (PHLHD). Current practice is to use right heart catheterisation (RHC) to distinguish between the two conditions. We explored the use of left atrial volume (LAV) obtained via cardiac magnetic resonance imaging (CMR) as an alternative to RHC.
Methods: Patients being admitted for diagnostic assessment underwent CMR and RHC. LA volume was assessed using standard 2- and 4-chamber CMR views and the biplane area-length method, and indexed to the body surface area. RHC was then performed within 72 hours. IPAH was defined as per current guidelines. Patients with mean PAP >25mmHg and PAWP >15mmHg at RHC were considered to have PHLHD.
Results: Between Jan 2009 and Feb 2011 we diagnosed 31 patients with IPAH (mPAP 47±10, PAWP 7±4 mmHg) and 19 patients with PHLHD (mPAP 43±8, PAWP 22±6 mmHg). LAV was significantly lower in IPAH compared with PHLHD (24±9 ml/m^2 vs 66±19 ml/m^2, p<0.0001). Using an LAV threshold of 43 ml/m^2

as the cutoff, we could distinguish IPAH from PHLHD with 97% sensitivity and 100% specificity. The area under the ROC curve was 0.99.



Conclusion: Left atrial volume of 43 ml/m^2 recorded by CMR may be a useful means of distinguishing between IPAH and PHLHD, avoiding the need for catheterisation.

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The changing picture of patients with pulmonary arterial hypertension (PAH) in France

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The PH Registry provides current demographics of patients (pts) with PAH in France. We describe clinical characteristics, haemodynamics and survival of pts newly diagnosed with PAH between Nov 06 and Oct 09.
Methods: Clinical and haemodynamic characteristics of all consecutive newly diagnosed pts (i.e. incident cases) belonging to groups 1 (PAH) and 1' (pulmonary veno-occlusive disease [PVOD]) were collected at the time of diagnosis. Survival was analysed from PAH diagnosis to a cut-off date of 1 Nov 10.
Results: A total of 751 pts were analysed. F/M sex-ratio was 1.26, mean (±SD) age was 56±15 yrs (18–86) and 24% of pts were > 70 yr. Idiopathic (I), heritable (H), anorexigen (An), connective tissue disease, congenital heart disease, portal hypertension, HIV and chronic haemolytic anaemia-associated PAH accounted for 38.3%, 2.4%, 4.8%, 19.6%, 4.7%, 16.6%, 4% and 0.7% of the population, respectively. Thirty five pts (4.7%) had 2 risk factors for PAH. PVOD was diagnosed in 4.3% of pts. At diagnosis, 74% of pts were in NYHA class III or IV. Mean 6-min walk was 335±123 m. Mean PAP, cardiac index and PVR were 47±12 mmHg, 2.6±0.9 L/min/m^2 and 741±413 dyn.s.cm^{-5}, respectively. PAH-specific therapies were initiated in 620 pts (82.6%). One-, 2- and 3-year survival estimates were 88.5%, 78.2% and 69.2% in the overall population, and 88.3%, 77.3% and 67.7% in the subgroup (n=350) with IPAH, HPAH or An-PAH, respectively.
Conclusions: PAH is still diagnosed late in the course of the disease. Furthermore, pts are older and the proportion of males is higher than that observed in other registries. Finally, there is a trend for an improved survival in pts with IPAH, HPAH or An-PAH compared to our previous findings.

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A genome wide DNA microsatellite association study of Japanese patients with high altitude pulmonary edema

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Introduction: High altitude pulmonary edema (HAPE) is a non-cardiogenic pulmonary edema that develops in susceptible people who ascend quickly to high altitude. The pathogenesis remains to be conclusively elucidated and genetic polymorphisms were highly proposed to be associated with HAPE. The aim of this study is attempt to identify the locations of the candidate human genes those might associate with the HAPE susceptibility or resistance.
Methods: The case group included 53 Japanese HAPE susceptible subjects (HAPE-s) who had developed HAPE during climbing mountains higher than 2500m and the control group enrolled 67 HAPE Japanese resistant subjects (HAPE-r) who were Japanese Alpinist and did not develop HAPE during their histories. A case-control association study was performed using 400 polymorphic microsatellite markers (which define about 10 centiMorgan resolution throughout the whole genome) by PCR. The PCR-amplified products were sequenced automatically by Gene Scan software.
Results: Nine markers (D1S468, D1S2697, D1S2785, D4S405, D5S424, D6S257, D12S2638, D16S3103 and D21S263) showed statistically significant associations with the susceptibility to HAPE, and three markers (D1S230, D14S283 and D22S280) showed significant associations with the resistance to HAPE. These markers were in linkage with genes controlling pulmonary alveolus structure, chloride channel, endocrine proteins, and other factors those might play important roles in the development of HAPE.
Conclusion: This is the first genomewide association study in HAPE. It revealed several candidate genes in associations with HAPE. The development of HAPE may be determined by the interaction of multiply genes.

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Predicting survival in pulmonary hypertension in the United Kingdom: Comparison of prognostic equations

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Background: Prognostic equations in pulmonary arterial hypertension (PAH) have been developed in the United States [1,2] and France [3]. It is not known if these would perform as well in the United Kingdom (UK) as a locally derived scoring scheme.
Aims: To develop and validate a UK composite score (CS) to predict prognosis in pre-capillary pulmonary hypertension (PCPH).
Methods: The CS was derived from 209 patients with PCPH (except congenital heart disease) treated in the Scottish Pulmonary Vascular Unit (2000-09) by including independent baseline prognostic variables identified in multivariate Cox analysis. Brier scores (BS) were used to compare its performance with other equations in 121 patients with PCPH treated at Papworth Hospital, UK. Superior performance was indicated by a lower BS.
Results:

Table 1. CS

		Points
Age (years)	<70	0
	≥70	1
Gender	Female	0
	Male	1
Aetiology	Idiopathic, familial and anorexigen-associated PAH or connective tissue disease associated PAH except scleroderma or distal chronic thromboembolic disease	0
	Scleroderma or other WHO Group I PAH not above	1
Transfer factor (% predicted)	≥60	0
	40–60	1
	<40	2
6-min walk distance (m)	≥300	0
	150–300	1
	50–150	2
	<50	3
Right atrial pressure (mmHg)	<10	0
	≥10	1
Cardiac output (L/min)	≥3	0
	<3	1

The risk of death increased with CS in the Papworth cohort (HR 1.5, p<0.0001). The CS had a significantly lower BS than REVEAL[1] (0.096 vs 0.114) and French Registry[3] equations (0.096 vs 0.126) at 1 year, and French Registry equation[3] (0.153 vs 0.200) at 2 years.
Conclusions: The CS predicts survival and appears to be superior to other equations in an independent UK cohort.
References:
[1] Benza et al. Circulation 2010.
[2] Thenappan et al. ERJ 2010.
[3] Humbert et al. ERJ 2010.

4916

Genetic counselling in pulmonary arterial hypertension: Experience from the French referal centre

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Background: Mutations in *BMPR2* gene and more rarely in *ACVRL1* and *ENG* genes are detected in patients displaying idiopathic pulmonary arterial hypertension (PAH), pulmonary veno-occlusive disease (PVOD) and in patients with a family history of PAH or PVOD.
Aims and objectives: To screen mutations in PAH-predisposing genes in patients from the French Referal Centre and to identify high-risk relatives carrying genetic mutations.
Results: Genetic counselling and testing were offered to 434 PAH patients (347 idiopathic and 87 familial) and to 66 PVOD patients (12 with a family history

of PVOD). Mutations in PAH predisposing genes were identified in 58 patients with idiopathic PAH (17%) (52 *BMPR2* and 6 *ACVRL1* mutations) and in 73 PAH patients with a family history of PAH (84%) (69 *BMPR2* and 4 *ACVRL1* mutations). A *BMPR2* mutation was identified in 2 PVOD patients with a family history of the disease (17%) and in only 1 PVOD patient without family history (2%).

Genetic screening was offered to 167 asymptomatic relatives of *BMPR2/ACVRL1* mutation carriers and a mutation was identified in 60 of them. These subjects, having a 10-20% risk of developing PAH, received clinical screening by echocardiography every 1 to 3 years and when symptoms such as exercise dyspnoea occur. We hypothesize that screening will allow early diagnosis and treatment of the disease and in turn improve patients' survival.

Conclusion: Systematic search of a mutation in PAH predisposing genes allowed us to identified 134 patients carrying a mutation. Half of them had no family history of PAH, suggesting the importance to propose genetic analysis to PAH and PVOD patients with and without family history of the disease.