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Inside this issue: Pulmonary Hypertension

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Plasma Metabolomics Implicate Modified Transfer RNAs and Altered Bioenergetics in the Outcome of Pulmonary Arterial Hypertension.

Rhodes CJ et al. Circulation. 2016 DOI:10.1161/CIRCULATIONAHA.116.024602.

http://circ.ahajournals.org/content/early/2016/11/21/CIRCULATIONAHA.116.024602.long

The ability to predict outcomes in patients with Pulmonary Arterial Hypertension (PAH) and develop new biomarkers to monitor progress needs refinement. A comprehensive study of plasma metabolites using ultra-performance liquid chromatography mass-spectrometry to (1) identify patients at high risk of early death, (2) identify patients who respond well to treatment and (3) provide novel molecular insights into disease pathogenesis was performed.

Fifty three circulating metabolites distinguished well-phenotyped patients with idiopathic or heritable PAH using the UK cohort (n=365) from healthy controls (n=121) following correction for multiple testing (p<7.3e-5) and confounding factors, including drug therapy, renal and hepatic impairment. A subset of 20/53 metabolites also discriminated PAH patients from disease controls (symptomatic patients without pulmonary hypertension, n=139). 62 metabolites were prognostic in PAH, with 36/62 independent of established prognostic markers. Increased levels of tRNA-specific modified nucleosides (N2,N2-dimethylguanosine, N1-methylinosine), TCA cycle intermediates (malate, fumarate), glutamate, fatty acid acylcarnitines, tryptophan and polyamine metabolites and decreased levels of steroids, sphingomyelins and phosphatidylcholines distinguished patients from controls. The largest differences correlated with increased risk of death and correction of several metabolites over time was associated with a better outcome. Patients who responded to calcium channel blocker therapy had metabolic profiles similar to healthy controls confirming that vasoreactive patients represent a very different disease profile. In summary metabolic profiles in PAH are strongly related to survival and should be considered part of the deep phenotypic characterisation of this disease. Our results support the investigation of targeted therapeutic strategies that seek to address the alterations in translational regulation and energy metabolism that characterize these patients.

Dynamic Risk Stratification of Patient Long-Term Outcome After Pulmonary Endarterectomy: Results From the United Kingdom National Cohort.

Cannon JE, et al., Circulation. 2016 May 3;133(18):1761-71

http://circ.ahajournals.org/content/133/18/1761.long

Chronic thromboembolic pulmonary hypertension results from incomplete resolution of pulmonary emboli. Pulmonary endarterectomy (PEA) is potentially curative, but residual pulmonary hypertension following surgery is common and its impact on long-term outcome is poorly understood. We wanted to identify factors correlated with poor long-term outcome after surgery and specifically define clinically relevant residual pulmonary hypertension post-PEA. This study examines data from the UK National PH collaborative.

Eight hundred eighty consecutive patients (mean age, 57 years) underwent PEA for chronic thromboembolic pulmonary hypertension. Patients routinely underwent detailed reassessment with right heart catheterization and noninvasive testing at 3 to 6 months and annually thereafter with discharge if they were clinically stable at 3 to 5 years and did not require pulmonary vasodilator therapy. Cox regressions were used for survival (time-to-event) analyses. Overall survival was 86%, 84%, 79%, and 72% at 1, 3, 5, and 10 years for the whole cohort and 91% and

90% at 1 and 3 years for the recent half of the cohort. The majority of patient deaths after the perioperative period were not attributable to right ventricular failure (chronic thromboembolic pulmonary hypertension). At reassessment, a mean pulmonary artery pressure of ≥30 mm Hg correlated with the initiation of pulmonary vasodilator therapy post-PEA. A mean pulmonary artery pressure of ≥38 mm Hg and pulmonary vascular resistance ≥425 dynes·s(-1)·cm(-5) at reassessment correlated with worse long-term survival.

Our data confirm excellent long-term survival and maintenance of good functional status post-PEA. Hemodynamic assessment 3 to 6 months and 12 months post-PEA allows stratification of patients at higher risk of dying of chronic thromboembolic pulmonary hypertension and identifies a level of residual pulmonary hypertension that may guide the long-term management of patients postsurgery

Initial combination therapy with ambrisentan and tadalafil and mortality in patients with pulmonary arterial hypertension: a secondary analysis of the results from the randomised, controlled AMBITION study.

Hoeper MM, et al., Lancet Respir Med. 2016 Nov;4(11):894-901.

http://www.sciencedirect.com/science/article/pii/S2213260016303071

In treatment-naive patients with pulmonary arterial hypertension, initial combination therapy with ambrisentan and tadalafil reduces the risk of clinical failure events compared with monotherapy. A secondary analysis was performed to further investigate the effect of combination therapy on survival.

Survival data was analysed from the modified intention-to-treat population of the Ambrisentan and Tadalafil in Patients with Pulmonary Arterial Hypertension (AMBITION) trial. AMBITION was a multicentre, randomised, double-blind study, in which treatment-naive patients with pulmonary arterial hypertension were randomly assigned in a 2:1:1 ratio and received combination therapy with ambrisentan and tadalafil, ambrisentan and placebo, or tadalafil and placebo. A prespecified analysis of all mortality events from randomisation to the end of the study, including patients who discontinued their assigned treatment was performed . In a post-hoc analysis, survival at 7 days after the termination of each individual patient's randomised treatment was analysed using Cox proportional hazard regression, Kaplan-Meier survival estimates, and the stratified log-rank test to compare the survival of patients receiving initial combination therapy or initial monotherapy.

The study population consisted of 605 patients with pulmonary arterial hypertension who were randomly assigned and received combination therapy (n=302) or monotherapy (n=303; 152 patients assigned to ambrisentan monotherapy and 151 patients to tadalafil monotherapy). At the end of the study, 29 (10%) of 302 patients in the combination therapy group had died compared with 41 (14%) of 303 patients in the monotherapy group (hazard ratio 0·67, 95% CI 0·42-1·08; stratified log-rank p=0·10). At 7 days after the end of randomised treatment, fewer patients had died in the combination therapy group (3 [1%] of 302 patients) compared with the monotherapy group (13 [4%] of 303 patients; hazard ratio 0·21, 95% CI 0·06-0·73).

These data indicate that initial combination therapy might be associated with a survival advantage compared with initial monotherapy in patients with newly diagnosed pulmonary arterial hypertension though should in no way be regarded as definitive. An important question still to be determined is whether we should be striving to identify a stratified approach to treating patients with PAH or continue using combination therapy.

The prognostic impact of thyroid function in pulmonary hypertension.

Richter MJ, et al., J Heart Lung Transplant. 2016 Dec;35(12):1427-1434

http://www.sciencedirect.com/science/article/pii/S1053249816301620

Thyroid disease is common in patients with pulmonary hypertension (PH), but its effect on long-term survival remains unknown. The prognostic significance of thyroid hormone levels of free triiodothyronine (fT3) and free thyroxine and thyroid-stimulating hormone (TSH), and thyroid hormone replacement (THR) therapy in PH was examined..

A retrospective analysis was performed in 1,756 patients enrolled in the Giessen PH Registry in 1999 to 2013 with baseline thyroid function data; of these, 355, 533, 498, and 370 had pulmonary arterial hypertension (PAH); including 192 with idiopathic PAH (iPAH), PH due to left heart disease, PH due to lung diseases, and chronic thromboembolic PH (CTEPH), respectively. Thyroid function parameters associated with mortality were identified using Cox regression and Kaplan-Meier analyses.

Transplant-free survival at 1, 3, and 5 years was 86.7%, 65.6%, and 53.0%, respectively. Absence of THR therapy was an independent predictor of death in iPAH (multivariate hazard ratio [HR], 2.50; 95% confidence interval [CI], 1.06-5.75). In patients without THR therapy, TSH levels in the lowest and highest quartiles (compared with the middle 2 quartiles) independently predicted death in iPAH (HR, 1.98; 95% CI, 1.07-3.67), whereas reduced fT3 levels were independently associated with increased death in PAH (HR, 8.30; 95% CI, 2.50-25.00) and CTEPH (HR, 1.79; 95% CI, 1.14-4.20).

Thyroid hormone levels and THR therapy are prognostic factors in iPAH, PAH, and CTEPH. Prospective studies are warranted to verify the prognostic significance of thyroid function and the effect of THR therapy in PH.
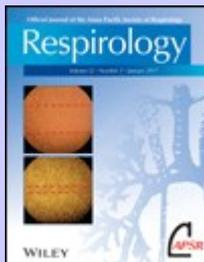
Endovascular treatment for chronic pulmonary hypertension: a focus on angioplasty for chronic thromboembolic pulmonary hypertension.

Satoh T, et al., Expert Rev Cardiovasc Ther. 2016 Sep;14(9):1089-94.

http://www.tandfonline.com/doi/full/10.1080/14779072.2016.1208083

Percutaneous transluminal pulmonary angioplasty (PTPA) was introduced for the treatment of chronic thrombo-embolic pulmonary hypertension (CTEPH) in the late 20(th) century, and first attempts in collective patients were made in 2001 with beneficial effects but a moderate amount of complications. It was refined around 2010, and has been recently established as an effective and safe treatment.

This review provides a useful recent state of the art base for learning.

There is considerable global interest in this procedure and attempts being made to identify which patients may be best suited for this form of therapy compared to PEA surgery.

The lesion best suited is typically a meshwork-like structure of organized thrombi and is sometimes not seen as a stenosis angiographically, necessitating other means of investigation such as measurement of distal pressure. The technique to treat lesions is the same as for coronary angioplasty except in several ways. The effects of PTPA may well be comparable to those of surgical endarterectomy, and the complications of reperfusion pulmonary edema and vascular injury are now controlled by several strategies and based on experience

MicroRNA-140-5p and SMURF1 regulate pulmonary arterial hypertension.

Rothman AM, et al., J Clin Invest. 2016 Jul 1;126(7):2495-508

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4922709/

Loss of the growth-suppressive effects of bone morphogenetic protein (BMP) signaling has been demonstrated to promote pulmonary arterial endothelial cell dysfunction and induce pulmonary arterial smooth muscle cell (PASMC) proliferation, leading to the development of pulmonary arterial hypertension (PAH). MicroRNAs (miRs) mediate higher order regulation of cellular function through coordinated modulation of mRNA targets; however, miR expression is altered by disease development and drug therapy thus inhibiting use of treated human subjects with PAH in evaluating the potential importance of these in our understanding of disease pathogenesis. Accordingly treatment-naive patients and experimental models of PAH were studied identifying a reduction in the levels of miR-140-5p. Inhibition of miR-140-5p promoted PASMC proliferation and migration in vitro. In rat models of PAH, nebulized delivery of miR-140-5p mimic prevented the development of PAH and attenuated the progression of established PAH. Network and pathway analysis identified SMAD-specific E3 ubiquitin protein ligase 1 (SMURF1) as a key miR-140-5p target and regulator of BMP signaling. Evaluation of human tissue revealed that SMURF1 is increased in patients with PAH. miR-140-5p mimic or SMURF1 knockdown in PASMCs altered BMP

signaling, further supporting these factors as regulators of BMP signaling. Finally, Smurf1 deletion protected mice from PAH, demonstrating a critical role in disease development. Together, these studies identify both miR-140-5p and SMURF1 as key regulators of disease pathology and as potential therapeutic targets for the treatment of PAH.

BMPR2 mutations and survival in pulmonary arterial hypertension: an individual participant data meta-analysis.

Evans JD, et al., Lancet Respir Med. 2016 Feb;4(2):129-37

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4737700/

Mutations in the gene encoding the bone morphogenetic protein receptor type II (BMPR2) are the commonest genetic cause of pulmonary arterial hypertension (PAH). However, the effect of BMPR2 mutations on clinical phenotype and outcomes remains uncertain.

Accordingly individual participant data of 1550 patients with idiopathic, heritable, and anorexigen-associated PAH from eight cohorts that had been systematically tested for BMPR2 mutations was studied. The primary outcome was the composite of death or lung transplantation. All-cause mortality was the secondary outcome. Hazard ratios (HRs) for death or transplantation and all-cause mortality associated with the presence of BMPR2 mutation were calculated using Cox proportional hazards models stratified by cohort.

Overall, 448 (29%) of 1550 patients had a BMPR2 mutation. Mutation carriers were younger at diagnosis (mean age 35·4 [SD 14·8] vs 42·0 [17·8] years), had a higher mean pulmonary artery pressure (60·5 [13·8] vs 56·4 [15·3] mm Hg) and pulmonary vascular resistance (16·6 [8·3] vs 12·9 [8·3] Wood units), and lower cardiac index (2·11 [0·69] vs 2·51 [0·92] L/min per m(2); all p<0·0001). Patients with BMPR2 mutations were less likely to respond to acute vasodilator testing (3% [10 of 380] vs 16% [147 of 907]; p<0·0001). Among the 1164 individuals with available survival data, age-adjusted and sex-adjusted HRs comparing BMPR2 mutation carriers with non-carriers were 1·42 (95% CI 1·15-1·75; p=0·0011) for the composite of death or lung transplantation and 1·27 (1·00-1·60; p=0·046) for all-cause mortality. These HRs were attenuated after adjustment for potential mediators including pulmonary vascular resistance, cardiac index, and vasoreactivity. HRs for death or transplantation and all-cause mortality associated with BMPR2 mutation were similar in men and women, but higher in patients with a younger age at diagnosis (p=0·0030 for death or transplantation, p=0·011 for all-cause mortality).

Patients with PAH and BMPR2 mutations present at a younger age with more severe disease, and are at increased risk of death, and death or transplantation, compared with those without BMPR2 mutations. The role of routine genetic testing for BMPR2 mutations on the management of patients with PAH deserves further study.

Pulmonary Arterial Hypertension: A Current Perspective on Established and Emerging Molecular Genetic Defects.

Machado RD, et al., Hum Mutat. 2015 Dec;36(12):1113-27

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4822159/

Pulmonary arterial hypertension (PAH) remains a fatal disorder resulting from several causes including heterogeneous genetic defects. While mutations in the bone morphogenetic protein receptor type II (BMPR2) gene are the single most common causal factor for hereditary cases, pathogenic mutations have been observed in approximately 25% of idiopathic PAH patients without a prior family history of disease. Additional defects of the transforming growth factor beta pathway have been implicated in disease pathogenesis. Specifically, studies have confirmed activin A receptor type II-like 1 (ACVRL1), endoglin (ENG), and members of the SMAD family as contributing to PAH both with and without associated clinical phenotypes. Current therapeutic approaches are based on targeting the prostaglandin, nitric oxide and endothelin pathways but novel new approaches addressing new targets are required. Most recently, next-generation sequencing has identified novel, rare genetic variation implicated in the PAH disease spectrum. Of importance, several identified genetic factors converge on related pathways and provide significant insight into the development, maintenance, and pathogenetic transformation of the pulmonary vascular bed. Together, these analyses represent the largest comprehensive compilation of BMPR2 and associated genetic risk factors for PAH, comprising known and novel variation. This article represents an excellent state of the art review of this evolving area

Diagnosis, Treatment, and Clinical Management of Pulmonary Arterial Hypertension in the Contemporary Era: A Review.

Maron BA and Galiè N., JAMA Cardiol. 2016 Nov 16 doi: 10.1001/jamacardio.2016.4471. epub

http://jamanetwork.com/journals/jamacardiology/article-abstract/2584721

Pulmonary arterial hypertension (PAH) is characterized by severe remodeling of the distal pulmonary arteries, increased pulmonary vascular resistance, and right ventricular dysfunction that promotes heart failure. Once regarded as largely untreatable, evidence-based decision making now guides clinical management of PAH and improves outcomes. However, misconceptions regarding the approach to PAH in the modern era are common and associated with substandard clinical care.

The clinical profile of PAH has changed substantially since its original description. Patients are older at diagnosis than previously reported; disease severity appears greater in men compared with women; and patients with PAH in association with connective tissue disease are identified as a particularly high-risk subgroup. Risk stratification scales for PAH are now available at point of care, which inform treatment goals, including a 6-minute walk distance of greater than 440 m, peak volume of oxygen consumption of greater than 15 mL/min/kg, right atrial area of less than 18 cm2, cardiac index of greater than 2.5 L/min/m2, and absent or low symptom burden with routine

physical activity. At present, 14 therapies targeting 6 PAH-specific molecular intermediaries are used clinically. Recent landmark trial data have demonstrated the critical importance of initial combination therapy in treatment-naive patients. These findings underscore a global shift in PAH that couples early disease detection with aggressive pharmacotherapy. Indeed, recent longitudinal data from patients receiving combination therapy show that the 3-year survival rate in PAH may be as high as 84% compared with 48% from the original National Institutes of Health registry on idiopathic PAH (1980-1985). Despite these gains, incomplete clinical evaluation and misdiagnosis by referring clinicians is common and associated with inappropriate therapy.

Compared with the original clinical experience, PAH has evolved into a contemporary and treatable disease characterized by improved survival and a high standard for defining therapeutic success. However, underawareness among clinicians regarding the importance of early and accurate PAH diagnosis persists and is a potentially reversible cause of adverse outcome in this disease.

Treprostinil Administered to Treat Pulmonary Arterial Hypertension Using a Fully Implantable Programmable Intravascular Delivery System: Results of the DelIVery for PAH Trial.

Bourge RC, et al., Chest. 2016 Jul;150(1):27-34.

http://www.sciencedirect.com/science/article/pii/S0012369215001609

The use of systemic prostanoids in severe pulmonary arterial hypertension (PAH) is often limited by patient/physician dissatisfaction with the delivery methods. Complications associated with external pump-delivered continuous therapy include IV catheter-related bloodstream infections and subcutaneous infusion site pain. An iv delivery system using a fully implantable pump would have potential benefits. A multicenter, prospective, single-arm, clinical trial (DelIVery for Pulmonary Arterial Hypertension) was conducted by using an implantable intravascular delivery system. The implanted pumps were refilled percutaneously at least every 12 weeks. The primary end point was the rate of catheter-related complications using the new model 10642 catheter compared with a predefined objective performance criterion of 2.5 per 1,000 patient-days based on the literature.

Patients (n = 60) with severe PAH (World Health Organization group 1) receiving a stable dose of IV treprostinil for at least 4 weeks received an implant device and were followed up for 12.1 ± 4.4 months. Six catheter-related complications occurred, corresponding to a complication rate of 0.27 per 1,000 patient-days. The 97.5% upper one-sided confidence bound of 0.59 was less than the predefined criterion of 2.5 per 1,000 patient-days (P < .0001). Plasma treprostinil levels at 1 week postimplantation were highly correlated with baseline levels (r = 0.91; P < .0001). The delivery system management time as reported by the patients was 2.5 ± 1.7 hours per week preimplantation, and this time decreased to 0.6 ± 0.8 hour per week at 6 months' postimplantation (P < .0001). All patients rated overall satisfaction with the implantable system as good, very good, or excellent at 6 weeks and 6 months. There were no catheter-related bloodstream infections or catheter occlusions.

The implantable intravascular delivery system delivered treprostinil to patients with PAH with a low rate of catheter-related complications and a high rate of patient satisfaction.

This method of drug delivery should now be considered in patients requiring intravenous prostaglandin therapy for PAH.

APSR Respiratory Updates is an initiative of the APSR Education Committee

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