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Inside this issue: Recent progress in the pathogenesis and management of pulmonary vascular diseases.

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Haemodynamic definitions and updated clinical classification of pulmonary hypertension.

Simonneau G et al.

Eur Respir J. 2019 Jan; 53(1): 1801913.

https://erj.ersjournals.com/content/53/1/1801913

Comments: This is a summary of the recommendations from the 6th World Symposium on Pulmonary Hypertension (WSPH) pertaining to haemodynamic definitions and the clinical classification of pulmonary hypertension (PH). The WSPH task force originally proposed that a mean pulmonary arterial pressure (PAP) of 20 mmHg be considered the upper limit of normal and that a pulmonary vascular resistance level >= 3 Wood units be included in the new definitions of all forms of pre-capillary PH, to discriminate an elevation in PAP caused by pulmonary vascular disease from that caused by PAWP elevation or high cardiac output. A change in the haemodynamic definition of PH does not always recommend treatment of these additional patients. Prospective trials are required to determine whether this altered PH population might benefit from specific management.

Regarding the clinical classification of pulmonary arterial hypertension (PAH), a subgroup referred to as “PAH long-term responders to calcium channel blockers” has been designated, because this specific PAH entity exhibits a distinct clinical course, characterised by a significantly better prognosis, unique management regimen and distinct pathophysiology. In addition, the subgroup “PAH with overt features of venous/capillary (pulmonary veno-occlusive disease/ pulmonary capillary haemangiomatosis) involvement” is included in the clinical classification of PAH due to evidence suggesting a continuum among arterial, capillary and venous involvement in PAH.

Genetic determinants of risk in pulmonary arterial hypertension: international genome-wide association studies and meta-analysis.

Rhodes CJ et al.

Lancet Respir Med. 2019;7(3):227-238

https://doi.org/10.1016/S2213-2600(18)30409-0

Comments: The authors conducted two genome-wide association studies (GWAS) and a meta-analysis of pulmonary arterial hypertension (PAH) to assess genetic variants affecting patient outcomes. A total of 5,895 whole-genome sequences were obtained from one of the GWAS, and genotyping array data were derived from the second GWAS.

The GWAS discovery analysis identified associations of loci located near SOX17 (rs10103692; odds ratio, 1.80 [95% CI 1.55–2.08], p=5.13 × 10-15) and HLA-DPA1/DPB1 (rs2856830; odds

ratio, 1.56 [1.42–1.71], p=7.65 × 10-20) with PAH, which was confirmed by the genome-wide meta-analysis. The conditional analysis showed that SOX17 possesses two polymorphisms (rs13266183 and rs10103692) related to gene regulation in endothelial cells. The C/C genotype of rs2856830 was related to a younger age at diagnosis and significantly worse survival compared with the other genotypes (log-rank p=0.011) among patients with PAH. It was also reported elsewhere that HLA-DPB1 is closely related to the development of chronic thromboembolic pulmonary hypertension without deep-vein thrombosis (J Hum Genet. 2009; 54:108–114).

Precision medicine approaches will potentially be facilitated by the discovery of these novel genes implicated in PAH. In addition, it appears that different subtypes of pulmonary hypertension are associated with common genetic factors.

Genomic comparison with supercentenarians identifies RNF213 as a risk gene for pulmonary arterial hypertension.

Suzuki H et al.

Circ Genom Precis Med. 2018 Dec;11(12):e002317.

https://www.ahajournals.org/doi/full/10.1161/CIRCGEN.118.002317

Comments: This study identified a candidate gene variant in the ATPase family member RNF213, p.Arg4810Lys, as a strong risk allele for pulmonary arterial hypertension (PAH) in Japanese individuals.

The authors performed a standard whole-exome analysis in two cohorts: 1) 76 Japanese patients with idiopathic PAH without BMPR2 expression and other known pathogenic gene mutations and 2) 79 Japanese supercentenarians without a past history of any significant health problems. The RNF213 p.Arg4810Lys variant was detected in the PAH cohort but was completely absent in the supercentenarians. Of the 76 patients with PAH, 7 (9.2%) harbored the variant, indicating a ratio of the frequency of this variant in idiopathic PAH relative to that in the normal Japanese population (0.7581%) of 6.0, according to the integrative Japanese Genome Variation Database.

RNF213 plays a critical role in angiogenesis and is a widely known susceptibility gene for moyamoya disease, a chronic progressive cerebrovascular disorder observed in East Asian populations. RNF213 variants are present in 90% of patients with moyamoya disease. In this study, the authors did not clarify the molecular functions of RNF213 variants.

Recently, Japanese cerebrovascular researchers revealed a role of RNF213 in the stabilisation of lipid droplets, suggesting a potential link between the pathogenesis of moyamoya disease and fat metabolism.

Clinical characteristics of RNF213 PAH patients should be investigated.

Bmpr2 mutant rats develop pulmonary and cardiac characteristics of pulmonary arterial hypertension.

Hautefort A et al.

Circulation. 2019 Feb 12;139(7):932-948

https://www.ahajournals.org/doi/full/10.1161/CIRCULATIONAHA.118.033744

Comments: This study characterised the first "Bmpr2 mutant rat" and showed that these rats exhibited some of the critical cellular and molecular dysfunctions described in human pulmonary arterial hypertension (PAH). Also, the heart was identified as an unexpected but potential target organ affected by Bmpr2 mutation.

Rats with a 71 bp monoallelic deletion in exon 1 (Δ71 rats) of Bmpr2 showed decreased Bmpr2 expression and phosphorylated SMAD1/5/9 levels. These Δ71 rats developed age-dependent spontaneous PAH with a low penetrance (16–27%), similar to PAH in humans. The Δ71 rats exhibited progressive pulmonary vascular remodeling associated with a proliferative phenotype and showed lower pulmonary microvascular density compared with wild-type Bmpr2 rats. Organ bath studies revealed severe alterations in pulmonary artery contraction and relaxation associated with potassium channel subfamily K member 3 dysfunction. Finally, detailed assessments of cardiomyocytes in these rats demonstrated alterations in morphology, calcium and cell contractility specific to the right ventricle; these changes could explain the lower cardiac output of Δ71 rats.

This new genetic rat model represents a promising powerful tool to study the pathogenesis of PAH in the future.

Selenoprotein P promotes the development of pulmonary arterial hypertension: A possible novel therapeutic target.

Kikuchi N et al.

Circulation. 2018;138:600–623.

https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.033113

Comments: The authors conducted for identifying a novel therapeutic target for PAH. Lung and serum samples from patients with PAH were screened using microarray analysis. The results showed a 32-fold increase in SeP expression in PAH PASMCs compared with control PASMCs. Moreover, high-throughput screening of 3336 low-molecular-weight compounds resulted in exploring a novel therapeutic agent (Sanguinarine) for treating a PH rat model. PASMC-specific SeP knockout mice and a PH rat model revealed a potential therapy against

SeP on PAH in vivo.

This study suggested that selenoprotein P (SeP) is a novel biomarker and therapeutic target of pulmonary arterial hypertension (PAH). Use of this biomarker may enable early diagnosis of PAH before the lesion develops resistance to currently used vasodilator drugs, to avoid the development of severe PAH.

Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives.

Humbert M et al.

Eur Respir J 2019;53:1801887

https://erj.ersjournals.com/content/early/2018/10/11/13993003.01887-2018

Comments: Pulmonary hypertension remains an incurable condition, and the novel scientific knowledge obtained pertaining to this condition requires translation to the clinic. This report reviewed the recent advances in pulmonary hypertension research. The authors described the pathological features of pulmonary arterial hypertension (PAH), including plexiform lesions, remodeling in pulmonary veins and the impact of bronchopulmonary anastomoses. The authors also showed recent advances in cellular abnormalities, such as dysfunction of pulmonary vascular endothelial cells, accumulation of pulmonary artery smooth muscle cells and adventitial fibroblasts, dysregulation of the innate and adaptive immune system.

Decades of extensive studies have also revealed the genetic, epigenetic and environmental factors leading to dysregulation of growth factors, ion channels, hormones and cytokines that subsequently cause abnormal vascular cellular phenotypes. However, translating pre-clinical discoveries into clinical testing is challenging because PAH is a rare disease. The authors also discussed ways to introduce the new approaches gleaned from the laboratory into the clinic.

Effect of the pulmonary embolism rule-out criteria on subsequent thromboembolic events among low-risk emergency department patients.

Freund Y et al.

JAMA. 2018 Feb 13;319(6):559-566.

https://jamanetwork.com/journals/jama/fullarticle/2672630

Comments: The prevalence of pulmonary embolism (PE) is less than 1% in patients who are negative for the pulmonary embolism rule-out criteria (PERC). However, no prospective study has yet implemented these criteria, and conflicting results from European populations have prevented inclusion of PERC-based strategies in most guidelines or recommendations.

This noninferiority, cluster randomised crossover clinical trial assessed the safety of the PERC-based strategy. Patients with a low gestalt clinical probability of PE were included. In the PERC period, the diagnosis of PE was excluded, with no further testing, if all eight items of the PERC criteria were negative.

A total of 1749 patients completed the trial. The 3-month risk of a thromboembolic event in the PERC strategy versus conventional strategy group was 0.1% versus 0.0%, a difference that met the noninferiority criterion of 1.5%. The proportion of patients undergoing CT pulmonary angiography in the PERC strategy versus conventional strategy group was 13% versus 23% ($p < 0.001$). In the PERC strategy group, the median stay in the emergency department and rate of hospital admission were significantly reduced. Among patients with a very low risk of PE in the emergency department, the use of a PERC-based strategy did not lead to an inferior rate of subsequent thromboembolic events compared with the conventional strategy, and it was cost effective by reducing unnecessary examinations.

This strategy can be used to rule out PE in the emergency department.

Comparison of an oral factor Xa inhibitor with low molecular weight heparin in patients with cancer with venous thromboembolism: results of a randomized trial (SELECT-D).

Young AM et al.

J Clin Oncol. 2018 Jul 10;36(20):2017-2023.

https://ascopubs.org/doi/pdf/10.1200/JCO.2018.78.8034

Comments: This study aimed the efficacy and safety of ribaroxaban compared with low molecular heparin, which is gold standard treatment of pulmonary embolism due to active can-

cer. In this randomised, multicentre, open-label trial, 203 patients with active cancer who had symptomatic PE, incidental PE, or symptomatic lower-extremity proximal deep vein thrombosis were randomised to receive dalteparin or rivaroxaban

The 6-month cumulative rates of VTE recurrence were 11% (95% CI, 7–16%) with dalteparin and 4% (95% CI, 2–9%) with rivaroxaban (hazard ratio [HR], 0.43; 95% CI, 0.19–0.99). The 6-month cumulative rate of major bleeding events was 4% (95% CI, 2–8%) with dalteparin and 6% (95% CI, 3–11%) with rivaroxaban (HR, 1.83; 95% CI, 0.68–4.96). The corresponding rates of clinically relevant non major bleeding events were 4% (95% CI, 2–9%) and 13% (95% CI, 9–19%), respectively (HR, 3.76; 95% CI, 1.63–8.69).

Following the Hokusai VTE Cancer trial, which showed noninferiority of edoxaban to low-molecular-weight heparin, this study demonstrated that rivaroxaban reduced the rate of VTE recurrence in patients with VTE and cancer. On the other hand, bleeding rates were increased in the rivaroxaban group.

Careful discussions about the benefits and risks are needed before using rivaroxaban for VTE with cancer.

The ADAMTS13-VWF axis is dysregulated in chronic thromboembolic pulmonary hypertension.

Newnham M et al

Eur Respir J. 2019 Jan 17.

https://erj.ersjournals.com/content/53/3/1801805

Comments: This study investigated the role of the ADAMTS13–VWF axis in chronic thromboembolic pulmonary hypertension (CTEPH), including its relationship to disease severity, inflammation, ABO group and ADAMTS13 genetic variants.

ADAMTS13 and VWF plasma antigen levels were measured in patients with CTEPH (n=208), patients with chronic thromboembolic disease without pulmonary hypertension (CTED; n=35) and healthy controls (n=68). ADAMTS–VWF axis abnormalities were assessed by measuring ADAMTS13 activity, D-dimer levels and VWF-multimeric size.

Patients with CTEPH had decreased ADAMTS13 (adjusted β (95% CI) = −23.4 (−30.9 to −15.1)%, p<0.001) and increased VWF (+75.5 (44.8 to 113)%, p<0.001) levels compared with healthy controls. The ADAMTS13 level remained low after treatment of pulmonary hypertension with pulmonary endarterectomy and was comparable with that in patients with CTED. Moreover, the authors identified a genetic variant near the ADAMTS13 gene associated with the ADAMTS13 protein that accounted for ~8% of the variation in levels.

The ADAMTS13-VWF axis is dysregulated in CTEPH, and this is unrelated to pulmonary hyper-

tension, disease severity or systemic inflammation, implicating the ADAMTS13-VWF axis in CTEPH pathobiology. The ADAMTS13-VWF axis could predict the development of CTEPH from acute pulmonary embolism. Further consideration of this dysregulation might be needed for detecting biomarkers.

Subpleural perfusion predicts failure after balloon pulmonary angioplasty for nonoperable chronic thromboembolic pulmonary hypertension.

Taniguchi Y et al

CHEST 2018; 154(3):521-531

https://doi.org/10.1016/j.chest.2018.03.059

Comments: Small vessel disease is a major determinant of poor outcome after pulmonary endarterectomy for chronic thromboembolic pulmonary hypertension (CTEPH). Out-of-proportion pulmonary vascular resistance may indicate the presence of small vessel disease, but its evaluation is very subjective.

A previous study showed that poor subpleural perfusion (PSP) in the capillary phase of pulmonary angiography may be related to small vessel disease and a poor surgical outcome for CTEPH.

The authors investigated the association between PSP and BPA failure. They observed PSP in 46.7% of patients in the treatment failure group versus 13.9% in the treatment success group ($p = 0.003$). PSP was the only predictor of BPA failure in a multivariate analysis (OR: 4.02; 95% CI 1.17–13.89; $p = 0.028$). The authors concluded that PSP (15% of inoperable CTEPH patients) in the capillary phase, suggesting the presence of small vessel disease with diffuse distal thrombosis, is a predictor of BPA failure. Interestingly both operable and inoperable patients may have small vessel disease, and PSP in pulmonary angiography is useful for its prediction.

Treatment focusing on small vessel disease, such as distal thrombosis and pulmonary vascular remodelling, in unobstructed vessels and its prevention is needed.

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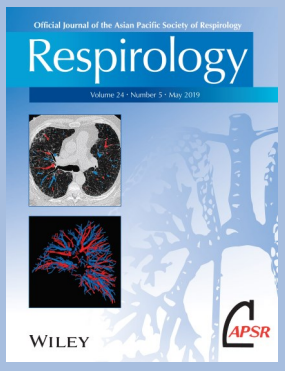

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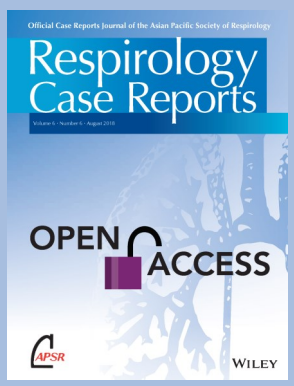

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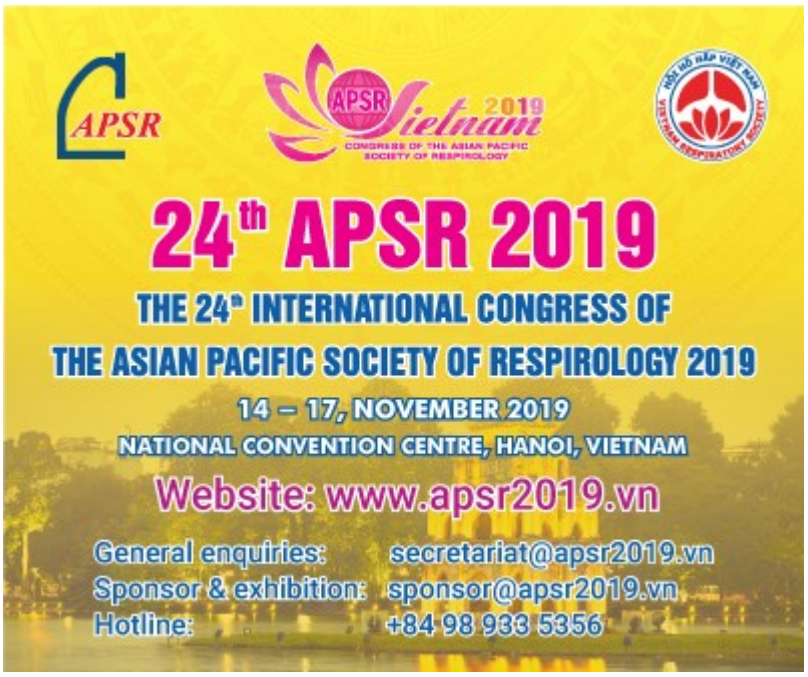

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