Respiratory RESEARCH REVIEW™

Making Education Easy

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In this issue:

Abbreviations used in this issue
BMI = body mass index
COPD = chronic obstructive pulmonary disease
CTEPH = chronic thromboembolic pulmonary hypertension
DVT = deep vein thrombosis
HR = hazard ratio
IPF = idiopathic pulmonary fibrosis
NYHA = New York Heart Association
PAH = pulmonary arterial hypertension
PAP/PAWP = pulmonary artery (wedge) pressure
PE = pulmonary embolism
PVR = pulmonary vascular resistance
VTE = venous thromboembolism

Welcome to this spring issue of Respiratory Research Review with the focus of VTE (venous thromboembolism) and pulmonary hypertension.

By the time you read through this selection, we will have elected a new government and will also be getting our minds around the referenda on cannabis and the end-of-life bill. I have enjoyed having more time exploring NZ, but I miss the opportunities to associate with my international colleagues at international conferences.

The 'Guidelines for the diagnosis and management of acute pulmonary embolism' (Respiratory Research Review, issue 165) were the hot topic at the last ERS conference. Following the publication of the guidelines, the scientific debate continues with publications like 'Should oral anticoagulation be discontinued after 3 months in the setting of a first high-risk pulmonary embolism secondary to a major transient/reversible risk factor?'. The data seem to be missing, and the authors argue for greater caution and prolonged anticoagulation, or a more individualised approach with no general prolonged anticoagulation. Another question debated is the role of 'Ventilation-perfusion SPECT (single-photon emission computed tomography) versus CTPA (CT pulmonary angiography) in young adult females with suspected pulmonary embolism'. Here a group of nuclear physicians from Denmark provide an excellent table of absorbed doses of radiation in the breast tissues, which varies 100-fold depending on the imaging modality. The main counterargument is the availability of ventilation-perfusion SPECT scanning. Finally, a trial in the Lancet caught my attention: 'Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT)'. It didn't find a clear survival benefit; however, there was a doubling of VTE events in the tranexamic acid group. Tranexamic acid should not be used for acute GI bleeding.

'Pulmonary hypertension by the method of Paul Wood' (Chest 2020) is written by John Newman from Nashville. He has the amazing ability to take a complex topic, explain it starting from basic principles and then addressing complex medical problems. At the end you are left wondering why you may have ever thought pulmonary hypertension is complicated; it is after all only the elevation in pressure not a diagnosis in itself. He has reached the scientific threshold attributed to Albert Einstein: *"Everything should be made as simple as possible, but no simpler"*. A group associated with IQVIA, known to many of us in NZ as a clinical trial co-ordinator, has published an 'Evidence synthesis in pulmonary arterial hypertension: a systematic review and critical appraisal'. As a clinician, the point/counterpoint debate on initial combination therapy for pulmonary arterial hypertension is probably a little easier to read. Marc Humbert and Edmund Lau argue 'Should initial combination therapy be the standard of care in pulmonary arterial hypertension? Yes', and Richard Channick and Rajan Saggar argue 'Should initial combination therapy be the standard of care in pulmonary arterial hypertension? No'. I am happy to be convinced otherwise; however, the Paris/Sydney team provide a better argument and sum it up in a beautiful diagram.

Hopefully, you enjoy the selection of articles and don't hesitate to contact me. I enjoy the exchange. You may enjoy this beautiful one-page case report highlighting the difficulties in diagnosing CTEPH (chronic thromboembolic pulmonary hypertension): 'Just because it walks like a duck, quacks like a duck, doesn't mean it can't be a goose!'.

Kind regards,

Professor Lutz Beckert
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Morbid obesity and mortality in patients with VTE

Authors: Giorgi-Pierfranceschi M et al., and the RIETE researchers

Summary: Using real-life clinical practice registry data (RIETE), these researchers evaluated how morbid obesity influences mortality in patients receiving anticoagulant therapy for VTE. Their analyses included 1642 patients who were morbidly obese and 14,848 who were normal bodyweight, for whom the respective proportions with cancer were 5.5% and 11.6%. Compared with normal bodyweight patients, those who were morbidly obese received a longer median duration of anticoagulant therapy both in those with cancer (185 vs. 114 days) and without cancer (203 vs. 177 days). Among patients with cancer, the respective mortality rates during anticoagulation for morbidly obese and normal bodyweight patients were 18.0% and 32.8% (multivariate HR 0.68 [95% CI 0.50, 0.94]), and among those without cancer, the respective rates were 3.1% and 5.6% (0.67 [0.49, 0.96]). There was no significant difference between morbidly obese and normal bodyweight patients for the risk of VTE recurrence or of major bleeding.

Comment: The WHO defines morbid obesity as a BMI >40 kg/m^2 and classifies it as a serious health condition. An increased BMI has been associated with an increased risk of cardiovascular disease; however, several studies have found an inverse relationship between an increased BMI and death, called the 'obesity paradox'. These Italian authors used the RIETE registry to explore the relationship between increased BMI, VTE and risk of dying. **Bottom line: the risk of dying of a VTE was about one-third lower in morbidly obese people compared with those with normal bodyweight.**

Reference: Chest 2020;157:1617–25
Abstract

Independent commentary by Professor Lutz Beckert

Professor Lutz Beckert is the Associate Dean Medical Education with the University of Otago, Christchurch. He is also a Respiratory Physician at Canterbury District Health Board. **FOR FULL BIO CLICK HERE**

Isolated pulmonary embolism is associated with a high risk of arterial thrombotic disease

Authors: ten Cate V et al.

Summary: These researchers from the prospective VTEval cohort study sought to determine if the presence of isolated PE signals a chronically elevated risk of arterial thrombotic disease; VTEval enrolled individuals with clinical suspicion and an imaging-based diagnosis or exclusion of VTE. Compared with patients with other PE phenotypes (n=447), those with isolated PE (n=63) had significantly greater prevalences of COPD, atrial fibrillation and coronary and peripheral artery diseases, and they had a greater incidence rate ratio of arterial thrombotic events (i.e., myocardial infarction, stroke/transient ischaemic attack) than those with DVT-associated PE (4.8 vs. 3.7 [p=0.001]).

Comment: This is another interesting insight from a patient registry, this time from Mainz in Germany. Many PEs arise from DVTs; while the DVT is not life threatening, the associated PE can have a 30% 30-day mortality rate. With increased scanning we also find isolated PEs without any evidence of DVT, often in segmental pulmonary arteries and associated with inflammatory illnesses likes COPD or asthma. Patients with isolated PEs had more atrial fibrillation, coronary artery disease and peripheral artery disease. **Bottom line: a PE without a DVT may be a risk factor for arterial thrombotic events, and screening for cardiovascular risk factors should be considered.**

Reference: Chest 2020;158:341–9
Abstract

Echocardiography-derived stroke volume index is associated with adverse in-hospital outcomes in intermediate-risk acute pulmonary embolism

Authors: Prosperi-Porta G et al.

Summary: Echocardiographic-derived variables including stroke volume index were retrospectively ascertained for normotensive patients admitted to hospital with an acute PE, among whom a primary outcome event (in-hospital PE-related death or cardiopulmonary decompensation) occurred in 3.9%. Each 1 mL/m^2 decrease in the stroke volume index increased the likelihood of a primary outcome event in a univariate logistic regression analysis (odds ratio 1.37 [95% CI 1.23, 1.52]), independent of age, sex, heart rate, tricuspid regurgitation velocity, tricuspid annular plane systolic excursion, troponin level and Bova score on bivariate logistic regression. Of all echocardiographic variables, stroke volume index had the highest C-statistic value (0.88), with a Youden's J-statistic that identified an optimal cutoff of 20.0 mL/m^2, corresponding to respective positive and negative likelihood ratios for a primary outcome event of 6.5 and 0.2.

Comment: A patient suffering a myocardial infarction without consideration of recanalisation or thrombolysis is virtually unthinkable today. In contrast, thrombolysis for a PE is rarely performed, partially because of lacking evidence and partially because of limited risk stratification tools. This group from Canada reports on more than 600 patients who had an intermediate risk PE and an echocardiogram for risk assessment. The authors report a strong correlation between echocardiographically assessed stroke volume and death or cardiopulmonary decompensation. **Bottom line: a risk score including echocardiographic assessment may in the future guide our PE treatment including thrombolysis.**

Reference: Chest 2020;158:1132–42
Abstract

Characteristics and long-term survival of patients with chronic thromboembolic pulmonary hypertension in China

Authors: Deng L et al.

Summary: The characteristics and long-term survival of patients with CTEPH treated with pulmonary endarterectomy (n=81), balloon pulmonary angioplasty (n=61) or medical therapy (n=451) were reported. The estimated respective overall 1-, 3-, 5- and 8-year survival rates were 95.2%, 84.6%, 73.4% and 66.6%, with rates of 92.6%, 89.6%, 87.5% and 80.2% in surgically treated patients and 95.4%, 88.3%, 71.0% and 64.1% in medically treated patients; the respective estimated 1-, 3-, 5- and 7-year survival rates for patients treated with balloon pulmonary angioplasty were 96.7%, 88.1%, 70.0% and 70.0%. Pulmonary endarterectomy was an independent predictor of survival.

Comment: CTEPH is caused by an obstruction of the pulmonary arteries with emboli, which leads to increased PVR (pulmonary vascular resistance) and progressive right heart failure. It may occur in up to 10% of patients following PE, and the prevalence may be as high as 20 per million. These authors from China report on almost 600 patients with CTEPH; of these about 15% received the preferred treatment of pulmonary endarterectomy, about 10% the emerging treatment of pulmonary angioplasty, and about 75% received PAH medications. **Bottom line: the 5-year outcome favoured pulmonary endarterectomy over angioplasty and medication use.**

Reference: Respirology; Published online Sept 20, 2020
Abstract

Exercise intolerance in chronic thromboembolic pulmonary hypertension after pulmonary angioplasty

Authors: Kikuchi H et al.

Summary: Relationships between exercise pulmonary hypertension and both exercise capacity and ventilatory efficiency were explored in patients with CTEPH who had normal resting haemodynamics following pulmonary balloon angioplasty. Compared with patients with nonexercise pulmonary hypertension (n=133), those with exercise pulmonary hypertension (n=116) had greater PVR at rest and lower peak oxygen consumption (13.5 vs. 16.6 mL/min/kg [p<0.001]). Mean PAP (pulmonary arterial pressure)-cardiac output slope negatively correlated with peak oxygen consumption (r=–0.45 [p<0.001]) and positively correlated with the minute ventilation versus carbon dioxide output slope (r=0.39 [p<0.001]).

Comment: In this fascinating study, Japanese researchers reported on 375 patients who had their CTEPH treated with balloon angioplasty. The patients underwent formal exercise testing using a ramp protocol with a cycle ergometer while having a right heart catheter *in situ*. The researchers provide a physiological answer to the observation that some patients with normal (resting) PAP describe ongoing exertional dyspnoea. Patients with normal resting pressure and ongoing breathlessness reached higher PAPs and lower cardiac outputs. **Bottom line: some patients with normal resting pressures following balloon angioplasty for CTEPH have increased PAP during exercise and impaired exercise capacity.**

Reference: Eur Respir J 2020;56:1901982
Abstract

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Diagnostic delay in pulmonary arterial hypertension: insights from the Australian and New Zealand pulmonary hypertension registry

Authors: Khou V et al.

Summary: Diagnostic delays for 2044 patients with PAH from the Australasian PHSANZ registry were reported for the 2004–2017 period. The median age at PAH diagnosis was 58 years, the female-to-male ratio was 2.8:1 and 82% of patients were NYHA functional class III or IV. The median time from symptom onset to diagnostic right heart catheterisation as entered in the registry (diagnostic interval) was 1.2 years. Independent predictors of a diagnostic interval >1 year were age, congenital heart disease PAH, obstructive sleep apnoea and peripheral vascular disease. Five-year survival was adversely impacted by a prolonged diagnostic interval. Diagnostic interval did not improve over the course of the study period.

Comment: These are data from our own pulmonary hypertension registry. Jason Weatherald and Marc Humbert point out in their editorial that there is room for improvement. In 2013, the average wait between the onset of symptoms and formal diagnosis was 3.9 years, and during this time the patient had on average five GP visits and three specialist visits. In 2018, the time to a right heart catheter shrunk to 1.2 years; however, one-third of patients still waited more than 2 years, and 25% waited more than 2.7 years. **Bottom line: patients waiting for more than 2 years for a diagnosis of pulmonary hypertension had worse outcomes.**

Reference: Respirology 2020;25:863–71
Abstract

Partial anomalous pulmonary venous drainage in patients presenting with suspected pulmonary hypertension

Authors: Lewis RA et al.

Summary: These authors reported on 90 registry patients with partial anomalous pulmonary venous drainage presenting to a pulmonary hypertension referral centre; 78% were newly diagnosed, despite 69% of these having undergone prior CT. A single right superior vein was affected in 67%, and a single left superior vein was anomalous in 23%. Right ventricular areas, pulmonary arteries and left-right shunts were larger and predicted diffusing capacity for carbon monoxide was significantly greater in patients with a sinus venosus atrial septal defect ($p<0.05$ for all). Pulmonary hypertension was diagnosed in 65 patients (postcapillary in 24). No additional causes of pulmonary hypertension were detected in 28 patients, 17 of whom (26% of those with pulmonary hypertension) had PVR of >3 Wood units. Isolated partial anomalous pulmonary venous drainage was present in seven of these patients, five of whom (8% of those with pulmonary hypertension) had anomalous drainage of a single pulmonary vein.

Comment: These are data from the British registry focussing on 90 patients with pulmonary hypertension who were noticed to have anomalous pulmonary venous drainage. Robert MacKenzie argues in his editorial that the clinician faces three challenges in patients with pulmonary anomalous drainage: i) to identify the abnormality, which may occur in about 0.5% of the population; ii) to perform appropriate pressure measurements in these patients; and iii) to determine when surgical correction is beneficial to the patient. **Bottom line: in patients with unexplained breathlessness, partial anomalous pulmonary venous drainage may be more common than we think.**

Reference: Respirology 2020;25:1066–72
Abstract

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Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension

Authors: Maron BA et al.

Summary: The relationship between PVR and adverse clinical outcomes in pulmonary hypertension was explored in a retrospective primary cohort of 40,082 US veterans (96.7% male; median age 66.5 years; 57.9% and 33.3% with heart failure and COPD histories, respectively) who had undergone right heart catheterisation and had median follow-up of 1153 days. The researchers focussed on 32,725 patients at risk for pulmonary hypertension (mean PAP ≥19mm Hg). When modelled as a continuous variable, there was an increased all-cause mortality hazard for PVR at ~2.2 vs. 1 Wood units. For PVRs ≥2.2 vs. <2.2 Wood units, patients with a mean PAP ≥19mm Hg and PAWP (pulmonary artery wedge pressure) ≤15mm Hg had increased risks for both mortality and heart failure hospitalisation (respective adjusted HRs 1.71 [95% CI 1.59, 1.84] and 1.27 [1.13, 1.43]). In a validation cohort (n=3699; 50.3% male; median age 60.4 years) with median follow-up of 1752 days, 2870 patients had mean PAP of ≥19mm Hg. In this cohort, patients with a mean PAP ≥19mm Hg, PVR ≥2.2 Wood units and PAWP ≤15mm Hg were at increased risk of death (adjusted HR 1.81 [95% CI 1.33, 2.47]).

Comment: We have previously reported that the World Symposium on pulmonary hypertension has adjusted the diagnostic criteria to be closer to the data originally described by Paul Wood. In this landmark study, a group of North American authors correlated right heart catheter pressure measurements of more than 40,000 patients with clinical outcomes at 1143 days. The authors discriminated patients with wedge pressure above and below 15mm Hg. **Bottom line: an increase in the PVR to more than 2.2 Wood units is associated with a sizeable increase in mortality risk, particularly in patients with a normal wedge pressure.**

Reference: Lancet Respir Med 2020;8:873–84
Abstract

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Respiratory Research Review

Pulmonary arterial hypertension with below threshold pulmonary vascular resistance

Authors: Ratwatte S et al., on behalf of the PHSANZ Registry

Summary: Eighty-two Australasian registry patients diagnosed with PAH with the predefined haemodynamic characteristics of mean PAP ≥25mm Hg, PAWP ≤15mm Hg and PVR <3 Wood units were studied in this research. The patients' underlying aetiologies included idiopathic disease (n=39), connective tissue disease (n=42) and human immunodeficiency virus infection (n=1). Mean PAP at diagnosis was 27mm Hg, PAWP was 13mm Hg, PVR was 2.2 Wood units, 6-minute walk distance was 352m and NYHA functional class was III–IV for 77% of the patients. Sixty-six patients started monotherapy with an endothelin receptor antagonist and 16 with a phosphodiesterase type-5 inhibitor. Six-minute walk distance had increased by 46m at the first re-assessment, and 35% of the patients had an improvement in their NYHA functional class. After a median 65 months of follow-up, the mortality rate was 22.0% (PAH-attributable mortality rate, 7%), with respective estimated 1-year and 5-year survival rates of 98% and 84%.

Comment: The previous article included 40,000 US patients with all causes for pulmonary hypertension; however, this article includes 82 patients with PAH with a 'borderline' increase of the mean PAP of 27mm Hg and a mean PVR of 2.2 Wood units. As Bradley Maron and Marc Humbert explain in their accompanying editorial, they add an important piece of the puzzle by demonstrating clinical improvement in PAH treatment across the spectrum of pulmonary hypertension. **Bottom line: patients with classical PAH features, but outside the diagnostic cutoffs, appear to respond well to PAH-specific therapy**.

Reference: Eur Respir J 2020;56:1901654
Abstract

Each month we highlight a particularly excellent paper with our butterfly symbol.

Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension

Authors: Behr J et al.

Summary: Patients aged 40–80 years with advanced IPF who were at risk of group 3 pulmonary hypertension were randomised to receive oral sildenafil 20mg (n=88) or placebo (n=89) three times daily, both added to oral pirfenidone 801mg three times daily, in this phase 2b trial. No significant difference was seen between the sildenafil and placebo arms for the proportion of participants with disease progression over 52 weeks (73% vs. 70% [p=0.65]). The respective serious treatment-emergent adverse event rates in the sildenafil and placebo groups were 61% and 62%, and the respective proportions who died due to treatment-emergent adverse events were 25% and 29%.

Comment: In the last issue of Respiratory Research Review (issue 177), we commented on the study showing no benefit of adding sildenafil to the treatment of IPF with nintedanib. This study is reporting similar negative results for adding sildenafil to pirfenidone in the treatment of IPF. The clinical pressure for these studies is high, since about 30–50% of patients with IPF will have pulmonary hypertension, which is associated with increased mortality and also symptoms of shortness of breath. However, the observed pulmonary hypertension may be a physiological compensatory mechanism. **Bottom line: no safety signals were identified adding sildenafil; however, no clinical meaningful improvements were noticed.**

Reference: Lancet Respir Med; Published online Aug 18, 2020
Abstract

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