Respiratory RESEARCH REVIEW™

Making Education Easy

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Abbreviations used in this issue

CTPA = computed tomography of pulmonary angiogram
DVT = deep vein thrombosis
HFPEF = heart failure with preserved ejection fraction
NYHA = New York Heart Association
OHCA = out-of-hospital cardiac arrest
PAH = pulmonary arterial hypertension
PE = pulmonary embolism
VTE = venous thromboembolism

Welcome to this autumn issue of Respiratory Research Review with the topics of VTE (venous thromboembolism) and PAH (pulmonary arterial hypertension).

At the time of writing, the world is in an ever-changing situation with regards to COVID-19, the illness caused by SARS-CoV-2. It is impossible not to be informed by the DHBs and NZ government. I also tend to keep an eye on these four websites: WHO, Nature, the CDC and JAMA. JAMA has shown real leadership of creating short podcasts, news items and videos tailored for doctors. The best information about COVID-19 for patients with lung disease is published by the European Lung Foundation.

'Running thin: implications of a heparin shortage' is a Lancet editorial highlighting our inter-connectedness and need for international collaborations. In 2000, about 12 million people were receiving heparin products with 80% of it being sourced from pigs in China. In 2007, the production was threatened by a respiratory illness called 'blue-ear pig' disease, leading to production shortage, degradation of the quality, and 81 people dying and several more injured by anaphylactic reactions in the USA. A decade later, the production is disturbed again by the outbreak of another virus, harmless to humans, causing internal haemorrhage in pigs and leading to a supply shortage caused by the African swine fever virus, which is spreading around the world. This editorial was written before the impact of the SARS-CoV-2 on the supply chain.

The birthday of the German pathologist and public health physician Rudolf Virchow, 13 October, has been chosen to be World Thrombosis Day (Intern Med J). While the public is currently acutely aware of the risk of COVID-19, there is also a more than 80% awareness of the risk of hypertension, breast/prostate cancer and AIDS. However, the awareness of DVT and PE was only 44% and 54%, respectively. Claire McLintock and Beverley Hunt from Auckland provide a short overview covering the risk of hospital-acquired VTE, its toll, particularly in middle-income countries, and the opportunity to contribute to reducing the noncommunicable disease by 25% in 2025.

In case you are pressed for time you may enjoy reading these three essentially one-page cases and essay:

- A teachable moment of a 76-year-old man who came to harm with well-intended bridging anticoagulation therapy – a primer to review the guidelines (JAMA Intern Med).
- Who would have thought that something could possibly go wrong when living off candy and sports drinks? Our colleagues from Boston report a fascinating case of 'Vitamin C deficiency-induced pulmonary arterial hypertension' (Chest).
- 'The gift' is the Wakley Prize Essay of an organ donation viewed through the eyes of the intensivist providing the care for the donor (Lancet). This essay left footprints in my soul.

The gift also provides the link to the concise clinical review 'Beyond the lungs: systematic manifestations of pulmonary arterial hypertension' (Am J Respir Crit Care Med). This international team of authors remind us that PAH, just like COPD, is defined/characterised by its lung involvement; however, PAH also exhibits vascular dysfunction in other organs and causes cerebral, skeletal muscle and kidney disease among others.

Thank you for all the feedback, it is greatly appreciated and one of the most enjoyable aspects of this review. Best wishes for the start of autumn.

Kind regards,

Professor Lutz Beckert
lutzbeckert@researchreview.co.nz

Covid-19 Response: Our heartfelt thanks

All of us at Research Review want to thank you for the part you are playing in the Covid-19 crisis. Our hats go off to you, and we are proud to be associated with you. Our role in all of this is to support you by keeping you informed and up to date as much as we possibly can.

Trends in mortality related to pulmonary embolism in the European Region, 2000–15

Authors: Barco S et al.

Summary: PE-related mortality and time trends across the European region were assessed in this analysis of vital registration data from the WHO Mortality Database for the 2000–2015 period. For the 41 member states from the WHO European Region with available data (n=650,950,921), the average number of PE-related deaths per year was 38,929 between 2013 and 2015. Among individuals aged 15–55 years, PEs were associated with 8–13 per 1000 deaths among females and 2–7 per 1000 deaths among males. There was a linear decrease between 2000 and 2015 in the age-standardised annual PE-related mortality rate from 12.8 to 6.5 per 100,000, with no notable sex-specific differences.

Comment: We are used to trending data over many years for about 300 diseases and injuries. According to these German authors, this was the first time these data were collated for 41 of the 53 member states of the WHO European Region, covering 650 million people for 16 years. The overall news is good; however, as the accompanying editorial points out, it is not clear whether this is due to an increased denominator (increased detection) or indeed better treatment and management. **Bottom line: the mortality of PE is decreasing. A PE remains a preventable cause of premature death.**

Reference: Lancet Respir Med 2020;8:277–87
Abstract

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

Clinical implications of incidental venous thromboembolism in cancer patients

Authors: Mulder FI et al.

Summary: Outcomes for participants from the Hokusai VTE Cancer Study with incidental (n=331) and symptomatic (n=679) VTE were reported; the study compared edoxaban with dalteparin for cancer-associated VTE. The respective median durations of anticoagulant treatment for participants with incidental and symptomatic VTE were 195 and 189 days. The proportion of participants with incidental VTE who experienced a composite primary outcome event (first recurrent VTE or major bleeding) was 12.7%, their major bleeding rate was 6.6% and their VTE recurrence rate was 7.9%; of the 26 VTE recurrences, five were incidental, seven were symptomatic and four were deaths for which PE could not be ruled out. The proportion of participants with symptomatic VTE who experienced a primary endpoint event was 13.8%, their major bleeding rate was 4.9% and their VTE recurrence rate was 10.9%. The groups had similar all-cause mortality rates.

Comment: As CT scanning improves and becomes more available for the diagnosis and monitoring of malignancy, so increases the chance of incidentally identified PEs. Up to half of all cancer-related PEs may be discovered on routine screening. These authors use data from a trial to assess the efficacy of oral edoxaban versus subcutaneous dalteparin. This trial had enrolled patients with incidental and symptomatic PEs. These patients had similar rates of recurrence and major bleeding. The accompanying editorial gives us the **bottom line: an incidental VTE, detected by chance, is still a VTE.**

Reference: Eur Respir J 2020;55:1901697
Abstract

Diagnosis of pulmonary embolism with D-dimer adjusted to clinical probability

Authors: Kearon C et al., for the PEGeD Study Investigators

Summary: In this prospective study of 2017 outpatients, PE was ruled out without further testing when the clinical pretest probability was low and the D-dimer level was <1000 ng/mL (n=1285) or when the clinical pretest probability was moderate and the D-dimer level was <500 ng/mL (n=40). Among these patients, including 315 with a low clinical pretest probability and a D-dimer level of 500–999 ng/mL, there were no VTEs during follow-up. The remaining patients underwent chest imaging (usually CTPA), and if PE was not diagnosed, they did not receive anticoagulation. Among those who were not diagnosed with PE initially and did not receive anticoagulation (n=1863), only one experienced a VTE. With this diagnostic strategy, a significantly lower proportion of patients underwent chest imaging compared with a strategy in which PE is considered to be ruled out with a low clinical pretest probability and a D-dimer level <500 ng/mL (34.3% vs. 51.9%; difference, –17.6 percentage points [95% CI –19.2, –15.9]).

Comment: This is a brilliant, short paper from Canada. The idea is so clear and simple, one wonders why we haven't done this before; however, this group managed to get it published in the N Engl J Med. They performed a prospective study on about 2000 patients with probable PE; all patients had a clinical risk assessment, D-dimer testing and a CTPA scan. **Bottom line: a PE is ruled out with a moderate pretest probability and a D-dimer level of less than 500 ng/mL. PE is also ruled out when the clinical pretest probability is low and the D-dimer level is less than 1000 ng/mL.**

Reference: N Engl J Med 2019;381:2125–34
Abstract

Thrombolysis during resuscitation for out-of-hospital cardiac arrest caused by pulmonary embolism increases 30-day survival

Authors: Javaudin F et al., on behalf of the Research Group of the French National Out-of-Hospital Cardiac Arrest Registry (GR-RéAC)

Summary: This retrospective study investigated 30-day survival in 246 evaluable adults from the French National Cardiac Arrest Registry with OHCA (out-of-hospital cardiac arrest) treated by a mobile ICU and with a hospital-confirmed diagnosis of PE. Among patients who received thrombolysis during resuscitation (n=58), 14 received alteplase, 43 received tenecteplase and one received streptokinase. Compared with patients who did not receive thrombolysis, those who did had a greater 30-day survival rate (16% vs. 6% [p=0.005]), but there was no significant between-group difference for good neurological outcome (10% vs. 5%; adjusted relative risk 1.97 [95% CI 0.70, 5.56]) or median ICU stay (1 day for both groups [p=0.23]).

Comment: The utility of thrombolysis treatment during an OHCA is uncertain. A PE is the underlying cause in 2–5% of cases. These French authors collected data on 85,000 patients with OHCA; a PE was confirmed in about 300 and they compared 58 patients who received thrombolysis with 188 patients who didn't. A clinician's suspicion of a PE was correct in about 75% of cases. The overall survival of an OHCA was 9%; the survival of PE-related OHCA was 16%. **Bottom line: patients with OHCA had a 30% increased survival when they received thrombolysis therapy during CPR.**

Reference: Chest 2019;156:1167–75
Abstract

Effect of osocimab in preventing venous thromboembolism among patients undergoing knee arthroplasty

Authors: Weitz JI et al.

Summary: The phase 2 open-label FOXTROT noninferiority trial randomised adults undergoing unilateral total knee arthroplasty to receive a single intravenous postoperative dose of osocimab 0.3 mg/kg (n=107), 0.6 mg/kg (n=65), 1.2 mg/kg (n=108) or 1.8 mg/kg (n=106), preoperative doses of osocimab 0.3 mg/kg (n=109) or 1.8 mg/kg (n=108), subcutaneous enoxaparin 40mg once daily (n=105) or oral apixaban 2.5mg twice daily (n=105) for ≥10 days or until venography; 600 of the randomised participants were included in the primary per-protocol analysis. The respective VTE incidences during postoperative days 10–13 (primary outcome) were 23.7%, 15.7%, 16.5% and 17.9% for the postoperative osocimab 0.3, 0.6, 1.2 and 1.8 mg/kg groups, 29.9% and 11.3% for the preoperative osocimab 0.3 and 1.8 mg/kg groups, and 26.3% and 14.5% for the enoxaparin and apixaban groups. When compared with enoxaparin, postoperative osocimab 0.6, 1.2 and 1.8 mg/kg met the noninferiority criterion (respective risk differences, 10.6% [one-sided 95% CI −1.2%, ∞], 9.9% [−0.9%, ∞] and 8.4% [−2.6%, ∞]), whereas preoperative osocimab 1.8 mg/kg was superior (15.1% [95% CI 4.9%, 25.2%]). The respective major or clinically relevant nonmajor bleeding rates among osocimab, enoxaparin and apixaban recipients were 4.7%, 5.9% and 2%.

Comment: Direct oral anticoagulants for stroke prevention have reduced the incidence of intracranial bleeding compared with warfarin. Nevertheless, bleeding is still a problem and the interest has moved to clotting factor XI as a target for anticoagulation. Preclinical studies suggest a significantly lower bleeding risk. This phase 2 study demonstrates that the humanised IgG1 monoclonal antibody, osocimab, which blocks factor XI activation, at a dose of 1.8 mg/kg is superior to standard treatment with enoxaparin or apixaban in preventing DVT; bleeding complications were low but similar in the groups. **Bottom line: osocimab is effective in preventing DVT; however, it is no safer than standard treatments.**

Reference: JAMA 2020;323:130–9
Abstract

Intensity and quality of exertional dyspnoea in patients with stable pulmonary hypertension

Authors: Boucly A et al.

Summary: These researchers evaluated the impact of dynamic changes in respiratory mechanics during exercise on qualitative dimensions of dyspnoea in 17 patients with clinically stable PAH and nine with chronic thromboembolic pulmonary hypertension who underwent incremental symptom-limited cycle exercise tests. The participants were defined as hyperinflators (65%) or non-hyperinflators (35%) based on changes in inspiratory capacity during the exercise tests. Hyperinflators exhibited a progressive decline in inspiratory capacity throughout exercise by 0.36L, whereas inspiratory capacity remained stable in non-hyperinflators. In a three-item questionnaire to assess dyspnoea quality during exercise, both groups selected the 'work/effort' descriptor most frequently (65% of all responses). At the inflection point of tidal volume relative to minute ventilation, a plateau was observed for selection of the 'work/effort' descriptor, while 'unsatisfied inspiration' descriptors were selected predominantly only in hyperinflators (77% of all responses). Anxiety was the emotion (from the affective domain) that was most frequently associated with dyspnoea.

Comment: Exertional dyspnoea is the commonest presentation of patients with idiopathic pulmonary hypertension and chronic thromboembolic pulmonary hypertension. These French researchers explored the mechanism of shortness of breath and the role of dynamic hyperinflation to trigger the sensation of dyspnoea by performing symptom-limiting exercise tests. This research provides rich insight into the physiology of breathlessness. The sensation of dyspnoea was independent of the underlying pathology and closely related to the lung mechanics and operating lung volumes. **Bottom line: interventions that reduce the ventilatory demand could delay hyperinflation and reduce symptoms of dyspnoea and anxiety in patients with pulmonary hypertension.**

Reference: Eur Respir J 2020;55:1802108
Abstract

Right ventricular-arterial uncoupling during exercise in heart failure with preserved ejection fraction: role of pulmonary vascular dysfunction

Authors: Singh I et al.

Summary: Invasive pulmonary haemodynamics, ventilation and gas exchange were recorded at rest and during exercise in 67 patients with HFPEF (heart failure with preserved ejection fraction) and 21 matched controls; 28 of the patients with HFPEF had an abnormal pulmonary vascular response during exercise. Marked decreases in peak VO_2 (oxygen consumption) and oxygen delivery and impaired chronotropic responses were seen in the patients with HFPEF with those with and without abnormal pulmonary vascular responses. In patients with HFPEF with normal pulmonary vascular responses, exercise was associated with a preserved end-systolic elastance response but a decrease in the ratio of end-systolic elastance response to pulmonary arterial elastance, while in those with abnormal pulmonary vascular responses, exercise-induced increases in end-systolic elastance were reduced, resulting in a decrease in the ratio of end-systolic elastance response to pulmonary arterial elastance and right ventricular-pulmonary artery uncoupling. Compared with HFPEF patients with normal pulmonary vascular responses, those with abnormal pulmonary vascular responses with an exercise-induced decrease in the ratio of end-systolic elastance response to pulmonary arterial elastance had lower pulmonary artery compliance, lower peak VO_2 and a lower stroke volume.

Comment: By far the largest number of patients presenting with shortness of breath and pulmonary hypertension have raised pulmonary pressures secondary to a stiff left ventricle/diastolic dysfunction/HFPEF. Our treatment algorithms for this large group of patients are not well established. This group of American researchers explored the role of an uncoupling of the right ventricle by analysing symptom-limiting exercise tests of more than 300 patients with HFPEF. **Bottom line: the right ventricle is markedly uncoupled from the pulmonary circulation leading the decreased exercise tolerance, offering a new target for therapeutic modalities.**

Reference: Chest 2019;156:933–43
Abstract

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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 with particular clinical interests in interstitial lung disease, pulmonary vascular disease, respiratory physiology and COPD (chronic obstructive pulmonary disease). Lutz is happy to be contacted to discuss research ideas either as a sounding board or with the view of future collaborations.

Retrospective validation of the REVEAL 2.0 risk score with the Australian and New Zealand Pulmonary Hypertension Registry cohort

Authors: Anderson JJ et al.

Summary: These researchers applied the REVEAL 2.0 risk score to a mixed prevalent and incident cohort of 1011 patients with PAH from the PHSANZ (Pulmonary Hypertension Society of Australia and New Zealand) registry. The REVEAL 2.0 model was found to effectively discriminate risk in this cohort both for the full eight-tier and three-category models (C statistic 0.74), and also when applied to incident cases only (C statistic 0.73). Robust separation of 12- and 60-month survival estimates were apparent with the three-category model ($p<0.001$ for all risk category comparisons). Although separation of low-, intermediate- and high-risk patients was seen with the full eight-tier model, there was overlap of survival estimates within some of the intermediate- and high-risk strata.

Comment: Large registries of patients with rare diseases like PAH can provide important insights into risk stratification, natural history and prioritisation of treatment. This is a collaboration of colleagues from Australia and NZ collating data from more than 1000 patients with right heart catheters, variables of the REVEAL criteria and 12 months follow-up. The REVEAL score is complex; however, it can be successfully applied to patients in Australia and NZ. Surprisingly, the overall survival is lower than those of other cohorts**. Bottom line: the Australian and NZ co-operation was successful, and one should work on a simplified score.**

Reference: Chest 2020;157:162–72
Abstract

Monitoring pulmonary arterial hypertension using an implantable hemodynamic sensor

Authors: Benza RL et al.

Summary: These researchers evaluated the feasibility and early safety of the CardioMEMS HF system (an ambulatory implantable haemodynamic monitor) for monitoring 26 patients with PAH and NYHA class III–IV right-sided heart failure. PAH therapy was safely monitored with the implanted sensors; there were no device-related serious adverse events and one preimplant serious adverse event. There was also a significant reduction in pulmonary artery pressure and an increase in cardiac output as early as 1 month postimplantation using trends of CardioMEMS HF data, along with significant improvements in NYHA class and quality of life within 1 year.

Comment: The prognosis of PAH remains poor with a survival rate of 68% at 3 years. However, it can be improved with goal-orientated treatment. Close monitoring is challenging in outpatient clinic settings and repeated right heart catheters are not feasible. These North American researchers report on the feasibility of an implanted monitoring system, which has been shown to improve survival in heart failure treatments. This proof-of-concept study confirmed the feasibility of noninvasive monitoring with only one complication. **Bottom line: if this can be shown to be effective in a controlled trial setting, it may meaningfully enhance the treatment of our patients with PAH.**

Reference: Chest 2019;156:1176–86
Abstract

Efficacy and safety of ralinepag, a novel oral IP agonist, in PAH patients on mono or dual background therapy

Authors: Torres F et al.

Summary: Patients with PAH managed with standard care, including mono- or dual PAH-targeted background therapy, were randomised to receive ralinepag starting at 10μg twice daily then titrated as tolerated to a maximum of 300μg twice daily (n=40) or placebo (n=21) in this phase 2 trial. Compared with placebo, ralinepag was associated with a significant decrease in pulmonary vascular resistance (–163.9 vs. +0.7 dyn·s/cm^5 [p=0.02]; least-squares mean change from baseline, –29.8% [p=0.03]). The respective increases in 6-minute walk distance in the ralinepag and placebo groups were 36.2m and 29.4m (p=0.90), the serious adverse event rates were 10% and 29%, and the study discontinuation rates were 13% and 10%.

Comment: The most effective treatment for PAH is prostacyclin, which via its receptor (IP) contributes to vasodilation, inhibition of smooth muscle proliferation, platelet inhibition, and is anti-inflammatory. The efficacy has been well proven; however, it is challenging to administer because of its poor bioavailability, instability and short half-life necessitating complex 24-hour infusion regimens. This is a phase 2 study of an orally available, non-prostanoid, selective IP agonist in 60 patients with PAH. It will move forward to a large-scale phase 3 study. **Bottom line: this new oral agent improves brain natriuretic peptide measurements, reduces pulmonary vascular resistance and is well tolerated even as add-on therapy.**

Reference: Eur Respir J 2019;54:1901030
Abstract