# Respiratory Research Review™

Making Education Easy

Issue 153 – 2018


## In this issue:



**Abbreviations used in this issue**
**ACE** = angiotensin-converting enzyme
**BNP** = brain natriuretic peptide
**CTEPH** = chronic thromboembolic PH
**CT/CTPA** = computed tomography (of pulmonary angiogram)
**$D_{LCO}$** = diffusing capacity of the lung for carbon monoxide
**ED** = emergency department
**IPF** = idiopathic pulmonary fibrosis
**PAH/PH** = pulmonary (arterial) hypertension
**PE** = pulmonary embolism
**RPVO** = residual pulmonary vascular obstruction
**VTE** = venous thromboembolism

# Welcome to this spring issue of Respiratory Research Review focussing on VTE (venous thromboembolic) disease and PAH (pulmonary arterial hypertension).

I have just completed a 3-month sabbatical period and, as part of my ongoing professional development, I have spent some time in the Pulmonary Arterial Hypertension service in Paris with Marc Humbert's group and at the Brompton. I am grateful that I have had this professional opportunity, and it has motivated me to continue staying up to date for the benefit of our patients.

The 'British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE)' led by Luke Howard draws the 'line in the sand' for our large number of patients with low-risk PE. The executive summary and editorial provide a 2-page overview of the key indications and pitfalls of outpatient management of PE.

Three review articles on the topic of VTE disease are worth highlighting before starting with the individual selection. Parth Rali and Gerard Criner from Pennsylvania assist us staying abreast of the research with a concise clinical review on 'Submassive Pulmonary Embolism'. Actually, there appears to be a transatlantic consensus that 'less is probably more', in the case of thrombolysis for PE (Thorax). We only have a good evidence base for thrombolysis in patients with massive PE without an increased risk of bleeding. A group from Oklahoma systematically applied a 'statistical fragility test' to some key findings in VTE management (Chest). Their main conclusion is that for a number of trials, it would have only taken one or two patients with a different clinical outcome to completely change the trial results. It is certainly interesting reading. Finally, David Garcia and Doruk Erkan publish a beautiful review article on antiphospholipid syndrome, an autoimmune disease which often, but not always, occurs as part of systemic lupus erythematosus.

The BMJ published a comprehensive and readable state-of-the-art review of the pathogenesis and treatment of PAH. The Joint National Institutes of Health Clinical Center and Pulmonary Hypertension Association Symposium published their report on the 'Challenges in pulmonary hypertension: controversies in treating the tip of the iceberg' with an excellent illustration on how to link clinical assessment, haemodynamic features and pathological phenotypes. Finally, and linking back to my opportunity to visit one of the leading PAH centres, colleagues, including the French team, spell out for us how the ability to identify and target low-risk profiles in PAH will lead to a paradigm shift toward goal-oriented clinical trial endpoints (Am J Respir Crit Care Med).

We hope you enjoy the selection of articles, and are looking forward to comments and feedback.

Kind regards


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Time spent reading this publication has been approved for CME for Royal New Zealand College of General Practitioners (RNZCGP) General Practice Educational Programme Stage 2 (GPEP2) and the Maintenance of Professional Standards (MOPS) purposes, provided that a Learning Reflection Form is completed. Please **CLICK HERE** to download your CPD MOPS Learning Reflection Form. One form per review read would be required.

Time spent reading this publication has been approved for CNE by The College of Nurses Aotearoa (NZ) for RNs and NPs. For more information on how to claim CNE hours please **CLICK HERE**.

## Management of low-risk pulmonary embolism patients without hospitalization

**Authors:** Bledsoe JR et al.

**Summary:** The Low-Risk Pulmonary Embolism Prospective Management study was conducted in five US EDs or hospitals and involved 200 adults diagnosed with acute PE who were assessed to be at low risk for mortality using the PESI (Pulmonary Embolism Severity Index) score (<86), echocardiography and whole-leg compression ultrasound. The study investigators sought to determine the 90-day composite rate of recurrent symptomatic VTE, major bleeding events and all-cause mortality among these patients. The participants were observed for 12–24 hours and then managed as outpatients with FDA-approved therapeutic anticoagulation. The primary outcome, a 90-day composite rate of all-cause mortality, recurrent symptomatic VTE and major bleeding, was 0.5% (one participant). There were no recurrent VTE cases or deaths during 90 days of follow-up. One participant experienced a major bleed. The participants reported that they were highly satisfied with their care.

**Comment:** This article and editorial echo the sentiment encapsulated by the British guidelines and editorial. The evidence base for outpatient management of PE in a select patient group is becoming more solid. Key criteria include identifying that patients are low risk, and do not have significant comorbidities like underlying malignancy. Integrating BNP and echocardiography findings as biomarkers is also possible. These authors have shown that they have been able to discharge over 200 patients from five EDs over 3 years without any PE recurrence or death, and only one major bleed. **Bottom line: in carefully selected patients with an acute PE and low-risk PESI, outpatient management is safe.**

***Reference: Chest 2018;154:249–56***
Abstract

## Preemptive anticoagulation in patients with a high pretest probability of pulmonary embolism: are guidelines followed?

**Authors:** Willoughby L et al.

**Summary:** This US research group reviewed the records of 3497 patients who underwent CTPA at two EDs to compare the time elapsed between ED registration and CTPA completion for patients with low, intermediate and high pretest probabilities for PE. Of 117 patients with a high pretest probability for PE, only two received pre-emptive anticoagulation. Moreover, among the remaining 115 patients with a high pretest probability for PE, 37 had a pre-existing indication for anticoagulation but did not receive pre-emptive anticoagulation. The time from ED registration to CTPA completion did not differ significantly based on the pretest probability of PE; median times from ED registration to CTPA completion were 187, 190 and 184 minutes for patients categorised as having low, intermediate and high pretest probabilities of acute PE, respectively.

**Comment:** So far we have focussed on how to identify low-risk patients and initiate outpatient treatment. Our guidelines also state that patients with a high pretest probability should be treated with anticoagulation while awaiting their diagnostic workup. Researchers from Salt Lake City reviewed 3500 consecutive cases from two EDs. They identified that about 5% of patients had a high pretest probability, and of these, a third had a pre-existing indication for anticoagulation. Yet, in only two cases pre-emptive anticoagulation was offered and diagnostic testing was not performed any sooner. **Bottom line: in patients at high risk of PE, treat first, diagnose later.**

***Reference: Chest 2018;153:1153–9***
Abstract

## Prognostic value of cardiovascular parameters in computed tomography pulmonary angiography in patients with acute pulmonary embolism

**Authors:** Beenen LFM et al.

**Summary:** Radiological and clinical data for 1950 randomised controlled trial participants with acute PE receiving anticoagulants were analysed to assess the effect of cardiovascular CTPA parameters (including right/left ventricular ratio, septal bowing, cardiothoracic ratio, diameters of pulmonary trunk and aorta and intrahepatic/azygos vein contrast medium backflow) on clinical outcomes in both the short- and long-term. Pulmonary trunk enlargement was found to be significantly associated with short-term (1-week) and long-term (1-year) mortality (respective odds ratios 4.18 [95% CI 1.04, 16.76] and 2.33 [1.36, 3.97]), as well as recurrent VTE and hospitalisation; no significant associations were seen for the other evaluated parameters.

**Comment:** This study from the Netherlands is probably going to be most helpful in the clinical environment I work in. The authors analysed radiological and clinical data on almost 2000 patients with acute PE who had participated in an international randomised controlled trial. They carefully correlated eleven cardiovascular radiological parameters, including right/left ventricular ratio, septal bowing, backflow into the azygous vein and others, at 1 week, 1 month or 1 year, with clinical outcome. Most associations with adverse outcomes were weak. **Bottom line: only increased size of the pulmonary trunk on CTPA is associated with increased short- and long-term mortality.**

***Reference: Eur Respir J 2018;52:1702611***
Abstract

## Prognostic impact of copeptin in pulmonary embolism

**Authors:** Hellenkamp K et al.

**Summary:** A *post hoc* analysis of data from 843 normotensive patients with PE from multiple European centres was conducted to validate the prognostic impact of copeptin level. The respective 30-day adverse outcome and PE-related mortality rates were 2.5% and 1.4%, with the respective risks significantly increased by factors of 6.3 and 7.6 among patients with a copeptin level of ≥24 pmol/L. There was a 5.6% risk of an adverse outcome among 248 patients classified as intermediate- to high-risk by the 2014 ESC (European Society of Cardiology) guideline algorithm, and an 8.9% risk among 123 meeting the same risk classification on a stepwise biomarker-based risk assessment strategy that considers high-sensitivity troponin T, N-terminal pro-BNP and copeptin levels. When copeptin level was incorporated into the ESC algorithm, identification of patients at higher risk of an adverse outcome and PE-related death was improved (respective odds ratios 11.1 [95% CI 4.6, 27.1] and 13.5 [95% CI 4.2, 43.6]), with 85 patients identified as having risks of 12.9% and 8.2%, respectively.

**Comment:** The articles selected so far highlight the great importance of risk assessment, e.g. for early discharge or pre-emptive treatment, and our poor performance in applying risk scores as health professionals. This may become the domain of neural networks or artificial intelligence in the future. In the meantime, this German group of researchers is exploring the role of biological markers to identify high-risk patients. In this paper, they are combining the stable surrogate marker of vasopressin, copeptin, which is released in cardiac stress and hypotension, with other risk stratification models. **Bottom line: copeptin in combination with BNP and troponin T identifies normotensive patients at risk of an adverse outcome.**

***Reference: Eur Respir J 2018;51:1702037***
Abstract



## Fibrinogen and the prediction of residual obstruction manifested after pulmonary embolism treatment

**Authors:** Planquette B et al.

**Summary:** The best models for predicting RPVO (residual pulmonary vascular obstruction) were selected using the Akaike Information Criterion and applied to two prospectively followed cohorts of 102 and 182 patients with acute PE; candidate variables used were the extent of the initial obstruction, clinical characteristics and fibrinogen-related data. The proportions of patients from the first and second cohorts with RPVO were 28.4% and 25.3%, respectively. The predictive model with the best fit derived in the first cohort, and validated in the second, showed that fibrinogen Bβ-chain monosialylation was involved in RPVO development. When clinical characteristics were excluded in the derivation analysis, fibrinogen Bβ-chain monosialylation remained a significant predictor of RPVO in the best-fit predictive model, whereas excluding fibrinogen characteristics led to worsening of the predictive model.

**Comment:** In the overwhelming majority, thrombotic material disintegrates in the pulmonary arteries after an acute PE. However, about 10% of patients tend to harbour RPVO, which can diminish physical activity and quality of life. About a third of these patients, approximately 3% of the total population, develop CTEPH (chronic thromboembolic PH). These French-American researchers detected RPVO in about a third of their cohort, and found a very strong association with a variant fibrinogen chain that is more resistant to fibrinolysis. **Bottom line: delayed resolution of PE causing development of CTEPH may be associated with a variant fibrinogen.**

***Reference: Eur Respir J; Published online Oct 18, 2018***
Abstract

## Multicentre observational screening survey for the detection of CTEPH following pulmonary embolism

**Authors:** Coquoz N et al.

**Summary:** A stepwise algorithm that included a phone-based dyspnoea survey, transthoracic echocardiography, right heart catheterisation and radiological confirmation was used to screen 508/1699 patients with acute PE for CTEPH at 6, 12 and 24 months in this prospective, multicentre, observational study. The incidence of CTEPH was 3.7 per 1000 patient-years in this group (2-year cumulative incidence, 0.79%). It was noted that additional CTEPH cases had not been reported in these patients in the Swiss PH registry in December 2016. The respective sensitivity and specificity values for the survey were 100% and 81.6%. Second-step echocardiography had a negative predictive value of 100% in patients with new dyspnoea.

**Comment:** In his editorial, Marius Hoeper questions that if between 10% and 30% of patients remain symptomatic with exertional dyspnoea after PE, should we systematically screen for CTEPH after acute PE? These Swiss researchers systematically followed 1700 patients with acute PE to answer this question. They excluded a large number of patients with pre-existing dyspnoea and CTEPH, and then investigated new dyspnoeic patients with echocardiography and a right heart catheter. **Bottom line: about 20% of patients developed dyspnoea after an acute PE; however, only 5% of the dyspnoeic and 1% of the total cohort developed CTEPH after 2 years.**

***Reference: Eur Respir J 2018;51:1702505***
Abstract



## The impact of patient choice on survival in chronic thromboembolic pulmonary hypertension

**Authors:** Quadery SR et al.

**Summary:** Outcomes and prognostic factors were reported for a cohort of 550 consecutive patients with CTEPH attending a UK centre during the 2001–2014 period. Nearly half the patients (49%) underwent surgery, 32% had operable disease but did not undergo surgery (72 patients by choice and 63 unfit), and 19% had inoperable disease because of disease distribution. Patients who underwent pulmonary endarterectomy had a greater 5-year survival rate than the inoperable patients and those with operable CTEPH who did not undergo surgery, including those who declined (83% vs. 53–59% [p<0.001]). Independent prognostic factors among patients who were offered pulmonary endarterectomy included decision to undergo the procedure, mixed venous oxygen saturation and gas transfer.

**Comment:** The 10-year survival of untreated CTEPH is about 10%, yet some patients with operable disease decline surgery. Nick Kim and Eckhard Mayer discuss why patients may not have endarterectomies, including due to delayed diagnosis of CETPH, no referral or no access to surgical centres. Researchers from Sheffield give us insight into what happens to patients without surgery. Half of their patients with CTEPH underwent surgery, and the other half: i) declined surgery; ii) were unfit for surgery; or iii) had other major contributors to breathlessness in addition to the clot burden. The 5-year survival in patients after surgery was 83%, and the 5-year survival in patients who declined surgery was 53%. **Bottom line: pulmonary endarterectomy is the lifesaving treatment of choice in CTEPH.**

***Reference: Eur Respir J 2018;52:1800589***
Abstract

## Incidence of pulmonary hypertension and determining factors in patients with systemic sclerosis

**Authors:** Coghlan JG et al.

**Summary:** This prospective study sought to evaluate the incidence of PH and identify determining factors in patients with systemic sclerosis and a $D_{LCO}$ value that was <60% of predicted. To achieve this, a cohort of 96 patients with mean baseline pulmonary arterial pressure <25mm Hg and who underwent right heart catheterisation were followed for a median of 3 years. A second right heart catheterisation was performed in 71 of the patients, and of this subgroup, 25.3% developed PH and 7% developed systemic sclerosis-associated PAH. Patients with a mean baseline pulmonary arterial pressure of 21–24mm Hg were significantly more likely to present with PH than normal pressures at follow-up (p=0.026). Independent predictors of PH during follow-up were pulmonary vascular resistance, tricuspid regurgitation velocity, diffusion capacity and inferior vena cava size at baseline.

**Comment:** Patients with scleroderma have a lifetime prevalence of PH of about 10%, and screening algorithms based on $D_{LCO}$ and echocardiography identify patients for right heart catheterisation. In this paper, the authors returned, 3 years later, to the initial cohort from the screening validation study, with a focus on patients who didn't have PH at the initial screening. A quarter of patients with scleroderma had developed PH; however, of these 18 patients, in five it was thought to be secondary to left heart disease and in eight due to lung disease. **Bottom line: regular clinical assessment including measurement of $D_{LCO}$ is justified in patients with scleroderma.**

***Reference: Eur Respir J 2018;51:1701197***
Abstract

## Likelihood of pulmonary hypertension in patients with idiopathic pulmonary fibrosis and emphysema

**Authors:** Jacob J et al.

**Summary:** The likelihood of PH was assessed in two consecutive cohorts of 223 and 162 patients with combined pulmonary fibrosis and emphysema who had undergone transthoracic echocardiography. The prevalences of increased likelihood of PH in the two cohorts were 29% and 31%. The 12-month survival rate across both cohorts was 60%; outcomes were not significantly worse for patients with IPF without emphysema. Total disease extent on CT was a predictor of PH, and when this was adjusted for, the association of combined pulmonary fibrosis and emphysema with PH was no stronger than it was for IPF without emphysema.

**Comment:** Emphysematous destruction of lung tissue and parenchymal replacement with fibrosis both reduce the vascular bed and lead to secondary PH (class III PH). Emphysema and IPF can co-exist, and PH has been found in up to half of these patients. Researchers from the Brompton and Mayo clinics reviewed their cohort of patients with emphysema and IPF to explore a possible synergistic effect on pulmonary vasculature. **Bottom line: the likelihood of having hypertension is related to the severity of emphysema and is not associated with a malignant microvascular phenotype.**

***Reference: Respirology 2018;23:593–9***
Abstract

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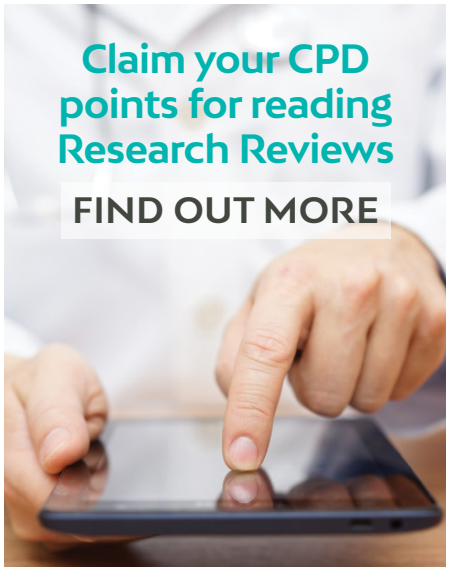

## A potential therapeutic role for angiotensin-converting enzyme 2 in human pulmonary arterial hypertension

**Authors:** Hemnes AR et al.

**Summary:** These researchers determined that: i) SOD-2 (superoxide dismutase 2) and inflammatory gene expression were markers of Mas receptor activation in porcine pulmonary arteries; and ii) plasma ACE-2 activity was reduced in human PAH by measuring conversion of angiotensin-2 to angiotensin 1–7. They then enrolled five patients with PAH to receive single intravenous infusions of recombinant human ACE-2 at doses of 0.2 or 0.4 mg/kg in a phase 2a, open-label pilot study. Recombinant human ACE-2 was associated with significant improvements in cardiac output and pulmonary vascular resistance, reduced plasma markers of inflammation within 2–4 hours and increased SOD-2 plasma protein levels at 2 weeks, and it was well tolerated.

**Comment:** This clinical phase 2a study in a small number of patients with PAH provides insight into the disease physiology with the potential for new treatment options for PAH. The accompanying editorial provides an illustration and explains the role of alternative ACEs to cleave angiotensin-1 into compounds with vasodilatory, anti-inflammatory and antiproliferatory properties. **Bottom line: the infusion of the recombinant human form of the naturally occurring ACE-2 was well tolerated, led to an improvement in pulmonary haemodynamics and a reduction in inflammatory markers.**

***Reference: Eur Respir J 2018;51:1702638***
Abstract

### Independent commentary by Professor Lutz Beckert.

Professor Lutz Beckert is the Head of Department of Medicine of 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 considering future collaborations.