Welcome to the March 2018 issue of Respiratory Research Review with a focus on VTE (venous thromboembolic disease), including DVT (deep vein thrombosis) and PE (pulmonary embolism), and also PAH (pulmonary arterial hypertension). Publications in this field far exceed the selection in this review and are a pleasure to read. None of the articles published are ground-breaking or disruptive; however, all of them address clinical questions we struggle with on a daily basis.

The focus is on addressing questions around biomarkers, tests during pregnancy, catheter-directed thrombolysis and the most effective treatments for VTE. The interested reader may enjoy browsing through some of the review articles and meta-analyses published, like the short three-page clinical update on DVT or ‘Pregnancy, thrombophilia, and the risk of a first venous thrombosis: systematic review and Bayesian meta-analysis’ (Galloway et al., BMJ). The take-home message is that women with antithrombin, protein C or protein S deficiency as well as women with homozygous factor V Leiden, but not heterozygous factor V Leiden or heterozygous prothrombin G20201A mutations, should be prescribed VTE prophylaxis. Alternatively one could read the systematic review and meta-analysis of ‘Prevalence and localisation of pulmonary embolism in unexplained acute exacerbations of COPD’. The authors’ take-home message is that a PE can be found on average in 16% of patients with unexplained exacerbations, and in around two-thirds of cases (68%) it is in the major pulmonary vessels.

The 6th World Symposium on Pulmonary Hypertension has just taken place in Nice from February 27 to March 1, 2018, and while some information has been ‘leaked’ on updated classifications, evidence-based treatments and an algorithm to detect diastolic dysfunction, we don’t expect a major revolution. However, we will have to wait for information to be peer reviewed before we can review it here. Hopefully the selection focusing on common clinical problems hits the mark. The interested reader may wish to browse the following two excellent reviews: ‘Update on chronic thromboembolic pulmonary hypertension’ (Trends Cardiovasc Med) on a condition that may be grossly underestimated in NZ, as the authors estimate we should see 112 per million cases, or just under 500 cases per year in NZ; and an authoritative review article by Sergio Harari, Davide Eila and Marc Humbert on ‘Pulmonary hypertension in parenchymal lung disease – any future for new therapies?’. In short, we are still looking and we remain hopeful about finding evidence-based treatment to at least treat the symptoms without increasing mortality.

We hope you enjoy the selection and are looking forward to your feedback.

Kind regards

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Independent commentary by Professor Lutz Beckert.

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FOR FULL BIO CLICK HERE
Association of lower diagnostic yield with high users of CT pulmonary angiogram

Authors: Chong J et al.

Summary: This retrospective review of 1394 CTPAs ordered by 182 physicians in Canada found that 14.3% were positive for PE. Using generalised estimating equations logistic regression, each additional 10 scans ordered per physician significantly decreased the likelihood of a PE-positive CTPA (odds ratio 0.7 [95% CI 0.73, 0.79]) and each 1-year increase in patient age increased the likelihood (1.02 [1.01, 1.03]). No significant change in likelihood was seen for physician experience, physician gender or emergency department-ordered scans. When the analysis was limited to 974 scans performed by emergency department physicians, 12.6% were positive, and similarly to what was seen for all scans) the likelihood of PE decreased as the number of scans ordered per physician increased.

Comment: The first audit from Australia showed diagnostic yield of 17% in CTPA scanning. In this audit from Canada the overall diagnostic yield was 14%, which compares well with published NZ data. The authors report that the doctor’s experience, sex and speciality had an influence on the diagnostic yield. The only variant explaining the diagnostic yield between 0% and 33% was the number of scans ordered. As highlighted in the commentary, this may reflect an overuse of CTPA scanning; however, the term ‘diagnostic yield’ is of limited value. Bottom line: the higher the number of CTPA scans ordered, the lower the diagnostic yield.


Abstract

Performance of low-dose perfusion scintigraphy and CT pulmonary angiography for pulmonary embolism in pregnancy

Authors: Sheen J-J et al.

Summary: This retrospective study compared low-dose perfusion scanning with CTPA in pregnant women requiring imaging studies for PE. Scans were positive for PE in 2.7% of initial low-dose perfusion scans (n=225) and 4.1% of initial CTPA scans (n=97), negative in 88.0% and 86.6%, respectively, and indeterminate/nondiagnostic in 9.3% and 9.3%, respectively; ten women were treated for PE. Low-dose perfusion and CTPA scans had respective NPVs of 100% and 97.5%. A subgroup analysis of the ~24% of patients with asthma revealed high likelihoods of negative studies in the low-dose perfusion scanning and CTPA groups (74.1% and 87.0%, respectively), with both modalities of 100% and 97.5%. A subgroup analysis of the ~24% of patients with asthma revealed high likelihoods of negative studies in the low-dose perfusion scanning and CTPA groups (74.1% and 87.0%, respectively), with both modalities of 100% and 97.5%.

Comment: Pregnancy is a risk factor for PE, and PEs are the cause of 9% of maternal deaths in the US. One needs to be mindful of the radiation exposure to the foetus (VQ [ventilation-perfusion] similar to CTPA after the first trimester) and to the maternal breast (lower in VQ scanning). Actually, one of the best evidence-based treatment algorithms was published in NZ. These American authors report compelling data on low-dose perfusion-only scans over two decades, with an NPV of 100%. Bottom line: low-dose perfusion-only scans cause less maternal and foetal radiation exposure and are a good first choice to exclude PE.

Reference: Chest 2018;153:152–60

Abstract

Predictive value of symptoms, signs and biomarkers on computed tomography pulmonary angiogram results

Authors: Sethwala A et al.

Summary: Medical records for patients who underwent a total of 150 CTPAs in Victoria, Australia, were analysed to determine which clinical parameters were used by clinicians to order the CTPAs and to establish which of these parameters were associated with the presence of PE. Twenty-five CTPA studies were positive for PE. Significant predictors of PE were prior VTE (p<0.0001), >1 VTE risk factor and a positive troponin test. Neither the presence nor the character of prior VTE were positive for PE. Significant predictors of PE were with the presence of PE. Twenty-five CTPA studies were used by clinicians to order the CTPAs and to were analysed to determine which clinical parameters underwent a total of 150 CTPAs in Victoria, Australia, summarised in the bottom line, one gets the impression that we ought to focus more on biomarkers in VTE:

Comment: This clinical audit from Geelong in Victoria reflects our status quo; PEs are found in 64% of those above the age of 65 years. Clinical examination added little; in particular chest pain and saturations were of no help. A previous VTE, a major risk factor and a positive troponin-T were the best predictors of VTE. Reflecting on the authors’ bottom line, one gets the impression that we ought to focus more on biomarkers in VTE. Bottom line: a raised troponin-T level increased the likelihood of a PE. No PE was detected in any patient with a negative D-dimer.


Abstract

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Risk factors for recurrent venous thromboembolism after unprovoked pulmonary embolism

Authors: Tronci C et al.

Summary: Risk factors for recurrent VTE following an unprovoked PE were evaluated in PADIS-PE trial participants randomised to 18 months of warfarin or placebo following 6 months of initial treatment. The VTE recurrence rate was 6.8 events per 100 person-years over median follow-up of 41 months, with the risk increased in participants aged 50–65 years (hazard ratio 3.65 [95% CI 1.33, 9.99]), those aged >65 years (4.70 [1.78, 12.40]), those with a PVOI (pulmonary vascular obstruction index) ≥5% at 6 months (2.06 [1.14, 3.72]), those with antiphospholipid antibodies (2.38 [1.15, 4.89]) and, considering nonavailability of PVOI at 6 months in practice, PVOI ≥40% at PE diagnosis (2-fold increased risk).

Comment: Patients who have had an unprovoked VTE are at increased risk of recurrence. If patients present with a PE, there is about an 80% likelihood they will re-present with a PE with a high case fatality rate. The risk can be reduced by lifelong anticoagulation, which will benefit the third of patients who would have a recurrence, but not the other two thirds. Here, the authors of the PADIS-PE study describe risk factors for recurrent VTE, which occurred in 20% of their patients. Bottom line: age above 65 years, antiphospholipid antibodies and a PVOI of more than 40% were independent predictors of recurrent VTEs.

Reference: Eur Respir J 2018;51:1701202

Abstract

Pharmacomechanical catheter-directed thrombolysis for deep-vein thrombosis

Authors: Vedanthan S et al., for the ATTRACT Trial Investigators

Summary: Patients with acute proximal DVT (n=692) were randomised to receive anticoagulation with (pharmacomechanical thrombolysis) or without (control) catheter- or device-mediated intrathrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration or maceration, with or without stenting. Compared with the control arm, pharmacomechanical thrombolysis was associated with: i) no significant difference for the proportion of patients who developed PTS (post-thrombotic syndrome) between 6 and 24 months (primary outcome; 47% vs. 48% [p=0.56]); ii) a higher 10-day major bleeding event rate (1.7% vs. 0.3% [p=0.049]); iii) no significant difference for VTE recurrence rate over 24 months (12% vs. 8% [p=0.09]); iv) a lower rate of moderate-to-severe PTS (18% vs. 24% [p=0.04]); v) lower Villalta PTS severity scores at 6, 12, 18 and 24 months (p<0.01 for all); and vi) no significant improvement from baseline in QOL at 24 months.

Comment: Patients with ongoing thrombus are at increased risk of recurrent PE and also at risk of PTS causing chronic pain, swelling, leg ulcers and reduction in QOL. These North American authors report a randomised trial of about 700 patients who either had routine treatment with anticoagulation or additional treatment with catheter-mediated intrathrombus delivery of recombinant tissue plasminogen activator and thrombus aspiration with or without stenting. As expected, the more invasive catheter-directed thrombolysis had more major bleeding episodes. Bottom line: catheter-directed thrombolysis did not lead to fewer cases of PTS.


Abstract

Age should not be a barrier for pulmonary endarterectomy in carefully selected patients

Authors: Nevinham M et al.

Summary: Outcomes were described for 1152 consecutive patients with CTEPH (chronic thromboembolic pulmonary hypertension) who underwent pulmonary endarterectomy. Among patients aged <80 years, the respective 1-, 3- and 5-year overall survival rates were 91.8%, 88.2% and 84.4%, and for those aged >80 years, they were 83.5%, 76.4% and 69.4%; survival in the older group was lower (p=0.020), but did not differ significantly from an age- and sex-matched reference population. Both age groups experienced significant improvements in WHO functional class, 6MWD and haemodynamics, with no significant differences between the age groups for median changes. The >80-year aged group had: i) significantly more concomitant cardiac surgical procedures, predominantly due to more coronary artery bypass grafts; ii) a shorter cardiopulmonary bypass time, but no difference in the total deep hypothermic circulatory arrest time or type of surgical disease; and iii) a longer length of hospital stay, but not ICU stay. No significant difference was seen for complications or inhospital mortality following pulmonary endarterectomy.

Comment: PEs are more common with advanced age and so is CTEPH. As pointed out in ‘Update on chronic thromboembolic pulmonary hypertension’ (Trends Cardiovasc Med), we can expect just under 500 cases in NZ and an endarterectomy is the treatment of choice. The Papworth unit in Cambridge has reported previously on their excellent results. Here they compared the outcomes of about 1000 patients under the age of 80 years with 37 patients aged over 80 years. Bottom line: in a highly selected group of octogenarians, an endarterectomy had similar improvements in survival, 6MWD and QOL.

Reference: Eur Respir J 2017;50:1701804

Abstract

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References.
1. Clexane® and Clexane® Forte Approved Data Sheet June 2017

VTE (Venous Thromboembolism), which is a combination of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) - CLICK HERE

For more information, please go to www.medsafe.govt.nz
Macitentan for the treatment of inoperable chronic thromboembolic pulmonary hypertension (MERIT-1)

Authors: Ghofrani H-A et al., on behalf of the MERIT study investigators

Summary: Patients with inoperable CTEPH (WHO functional class II–IV; PVR [pulmonary vascular resistance] >400 dyn·s·cm⁻¹ and 6MWD 165–440m) were randomised to receive oral macitentan 10mg (n=40) or placebo (n=40) once daily; PDE-5 inhibitor and oral or inhaled prostanoid therapy was permitted for participants in WHO functional class III or IV. Compared with placebo, macitentan was associated with a greater 16-week decrease in geometric mean PVR (by 73.0% vs. 8.7% of baseline [p=0.041]). The most common adverse events among macitentan recipients were peripheral oedema (23%) and decreased haemoglobin level (15%).

Comment: The methods section of this international trial is the most important aspect to appreciate in this article. Patients who were thought to be inoperable had a right heart catheter after 3 months of anticoagulation, pulmonary angiography and were discussed at an adjudication committee where the surgeon had performed at least 20 endarterectomies in the prior year (or 40 over 3 years).

As Adam Torbicki points out in the editorial, medical therapy is only appropriate if the patient has no operative option. Bottom line: inoperable patients with CTEPH reduced their PVR and improved their 6MWD on macitentan.


Abstract

RESPITE: switching to riociguat in pulmonary arterial hypertension patients with inadequate response to phosphodiesterase-5 inhibitors

Authors: Hoeper MM et al.

Summary: The RESPITE trial enrolled 61 patients with PAH (WHO functional class III, 6MWD 165–440m, cardiac index <3.0 L/min/m² and PVR >400 dyn·s·cm⁻¹), 82% of whom were receiving concomitant endothelin receptor antagonist, to remain free of PDE-5 inhibitor treatment for 1–3 days before receiving riociguat ≥2.5mg up to three times per day; 51 participants completed the trial. At week 24, mean 6MWD had increased by 31m, NT-proBNP level had decreased by 347 pg/mL and WHO functional class had improved in 54% of participants. The study drug-related adverse event rate was 52%, with a study drug-related serious adverse event rate of 3%; there were no serious adverse events during the PDE-5 inhibitor treatment-free period. Clinical worsening (including two deaths, unrelated to the study drug) occurred in 10% of participants.

Comment: In the accompanying editorial coauthored by Marc Humbert to this open-label study, the authors highlight the importance of this proof-of-concept study. A) The survival of PAH is still terrible and monotherapy is often insufficient for the majority of patients. B) Instead of adding medications, it is possible to swap an agent from the same group of medications. And C) is adding a medication always the right, automatic way to address a suboptimal response to therapy? Bottom line: selected patients with PAH may benefit from switching from sildenafil to riociguat.

Reference: Eur Respir J 2017;50:1602425

Abstract

Management and long-term outcomes of sarcoidosis-associated pulmonary hypertension

Authors: Boulcy A et al.

Summary: These researchers collected and analysed clinical and haemodynamic registry data from 126 patients with severe, newly diagnosed sarcoidosis-associated PH (mean pulmonary artery pressure >35mm Hg, or 25–35mm Hg with cardiac index <2.5 L/min/m²). PAH-targeted therapy was received by 97 patients, and immunosuppressive therapy was initiated or escalated in 33 at the time of PH diagnosis. PAH-targeted therapy was associated with a significant decrease in mean PVR from 9.7 to 6.9 Wood units after 4 months, with no significant improvement in exercise capacity. Among the patients treated only with immunosuppressive therapy (n=11), four experienced haemodynamic improvement, including two with compressive lymph node. Over median follow-up of 28 months, 39 patients required escalation of their PAH-targeted therapy, nine underwent lung transplantation and 42 died. The respective 1-, 3- and 5-year survival rates were 93%, 74% and 55%.

Comment: Sarcoidosis-associated PH is difficult to diagnose and difficult to manage. This report from the French registry of PH provides insights into 126 patients with sarcoidosis-associated PH. The sex ratio was 1:1, the average age of diagnosis was 58 years, most had stage IV disease and many had restricted lung function on spirometry. However, there was little agreement between lung function and PH, the delay in diagnosis was about 15 years and PH-specific treatment improved haemodynamics but not 6MWD. Bottom line: sarcoidosis-associated PH has a 5-year survival rate of 55%.

Reference: Eur Respir J 2017;50:1700465

Abstract

Survival of idiopathic pulmonary arterial hypertension patients in the modern era in Australia and New Zealand

Authors: Strange G et al., on behalf of PHSANZ Registry

Summary: Characteristics and survival outcomes over median follow-up of 26 months were reported for 220 consecutive Australasian registry patients with idiopathic, heritable or drug-induced PAH. Comorbidities included obesity (34.1%), systemic hypertension (30.5%), coronary artery disease (16.4%) and diabetes mellitus (19.5%). Fifty patients received initial dual therapy and four received initial triple therapy. The respective estimated 1-, 2- and 3-year survival rates were 95.6%, 87.3% and 77.0%. A multivariate analysis revealed that independent predictors of worse survival were male sex and lower 6MWD at diagnosis, whereas obesity was associated with better survival; other comorbidities did not significantly impact on survival. There was also a tendency for survival to be longer among patients who received initial dual oral combination therapy versus initial oral monotherapy (adjusted hazard ratio 0.27 [CI 0.06, 1.18]).

Comment: The final selection is also from a registry, our own Australian/NZ registry of consecutive cases of PAH. This database provides local data, suggesting an average age of 57 years at diagnosis with about 70% female predominance. Interestingly, obesity conveyed a small survival benefit; however, no survival difference was noted whether patients had first-line treatment with an endothelin receptor antagonist or PDE-5 inhibitor; patients on initial combination therapy had a nonsignificant trend for improved survival. Bottom line: our local survival data suggest 1-year and 3-year survival rates of patients with treated PAH to be 96% and 77%, respectively.

Reference: Heart Lung Circ; Published online Sept 19, 2017

Abstract

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