Editorial

Key topics in pulmonary vascular diseases (assembly 13) from the European Respiratory Society 2018 Parisian Congress

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Pulmonary vascular disease was a key topic at this years' European Respiratory Society Annual Congress and the first year of the creation of assembly 13. We therefore aim to concentrate on three key hot topics from the Congress and its impact on pulmonary vascular disease in clinical practice.

Risk assessment in pulmonary arterial hypertension (PAH)

Risk stratification is commonplace in other areas of medicine such as cardiovascular disease where it is an important part of clinical practice. It provides us with important information that helps guide diagnosis, and provides important prognostic information that allows us to tailor treatment to individual patients.

Risk prognostication in PAH is becoming increasingly common allowing clinicians to offer tailored care to the patient with PAH.

In 1991 a seminal paper by D'Alonzo *et al.* diagnosed 194 American patients with idiopathic pulmonary hypertension over a 4-year period, and suggested their mortality was closely linked to right ventricular function (1).

By measuring three parameters: mean pulmonary artery pressure, mean right atrial (RA) pressure and cardiac index (CI) a National Institute for Health equation was derived to help determine a PAH patient's prognosis. The authors themselves however stressed that the equation result should be used alongside other clinical parameters. A later study however, by Sandoval *et al.* demonstrated the utility of the NIH equation and discovered it to have a high sensitivity but poor specificity to predict survival (2).

Decades later, further risk scores have been developed demonstrating our improved understanding and management of the disease. The French Pulmonary Hypertension Network enrolled 354 patients with idiopathic, familial and anorexigen-associated PAH in their registry. A prognostic score was developed which included the variables gender, exercise capacity and cardiac output at diagnosis (3).

A few years later the Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management (REVEAL) registry prognostic equation was released and a subsequent risk score derived. REVEAL which is a multicenter US registry utilized 504 incident cases of idiopathic, familial and drug induced PAH to validate the equation and risk score which was developed from a cohort of 2,716 individuals. The REVEAL prognostic equation unlike the NIH equation included variables such as subclass of PAH, lung function and echocardiographic parameters (4). Unsurprisingly this equation was more accurate than the initial NIH prognostic equation.

The REVEAL risk score calculator derived from the equation also included clinical observations, renal dysfunction, diffusing capacity of the lung for carbon monoxide (DLCO), as well as the standard markers of right ventricular function and functional capacity. The score produced ranged between 0–22. Low risk patients having a predicted 1 year survival of 95–100%, 90–95% in the average group, 85–90% in the moderately high-risk group, 70–85% in the high-risk group and <70% in the very high-risk group (5).

In 2015 a joint collaboration between the US and French groups independently validated their risk equations and scores. The REVEAL risk score was applied retrospectively to the French cohort and the French risk equation to the REVEAL cohort. This demonstrated that both prognostic scores offered good calibration and accuracy in a different geographic population of PAH patients (6).

After such formative work the 2015 ERS/ESC guidance strongly recommended the use of risk assessment when evaluating patients. Akin to the REVEAL risk score this ERS/ESC assessment compromises of clinical, biochemical, imaging, haemodynamic data, and exercise capacity. This risk score was based on the evidence of known good prognostic factors conveying an improved prognosis, specifically: WHO functional capacity I–II, a 6-minute walk distance (6MWD) >440 m, RA pressure <8 mmHg, and a cardiac index (CI) >2.5 L/min/m^2, mixed venous oxygen saturations (SvO_2) >65% as well as brain natriuretic peptide (BNP) <50/N-terminal pro b-type natriuretic peptide (NT-pro BNP) <300 (7).

With an aim to simplify risk assessment the 2017 study by Boucly *et al.* ascertained in their cohort of 1,017 idiopathic, familial and drug induced PAH patients that four variables of WHO FC, 6MWD, RA pressure and CI allowed a clinician to ascertain transplant free survival at diagnosis and at the 12-month assessment of an individual.

The team interestingly also revealed that the presence of 'low risk' criteria at the 12-month assessment categorised patients at low long term risk, with improved diagnostic accuracy than a classification of low risk at presentation (8), these study findings were also found on a smaller scale in an earlier study by Nickel *et al.* (9).

At the ERS Congress this year Professor Sitbon introduced the results of a post hoc analysis from the GRIPHON study. It revealed the usefulness of prognostic and predictive value of risk assessment utilising the number of 'low risk' variables in the largest ever cohort of PAH patients.

Whilst it is widely accepted that the low risk category is associated with a superior prognosis, little data exists into what effect an improvement in functional outcome measures has, when they do not meet the low risk category threshold.

Therefore, it was especially pertinent that the American group presented a post hoc analysis of AMBITION trial pertaining to this. The group analysed 500 treatment naive patients and defining targets of a least a 40-metre improvement in 6MWD and a 600 ng/L drop in NT-pro BNP at 16 weeks. Of the remaining individuals who met these criteria the study demonstrated that despite not fully satisfying low risk criteria they still exhibited less unfavourable events.

Pulmonary venous thromboembolism

Acute pulmonary embolism is the third leading cause of vascular death. It can present either in isolation or in relation to underlying co-morbidities and its presentation often varies. This can often cause the clinician diagnostic quandaries and variability in the offered therapies. It's incidence has been estimated to be 0.95 per 1,000 population per year and the occurrence of PE events is almost a third of a million per year in the European Union (10).

At the ERS Congress the concept of pulmonary embolism response teams (PERT) was discussed. PERTs have been developed to offer standardised, patient specific therapy when presenting with an acute pulmonary embolism. Rapid risk stratification is of paramount importance and the first step in order to ascertain the optimal management strategy for acute PEs as discussed by Professor Sanchez at the ERS Congress.

The Pulmonary Embolism Severity Index (PESI) was initially developed and validated in 2005 (11). Its aim was to assess the risk of mortality and adverse events from a PE over 30 days, this study cohort included 15,752 patients with a confirmed PE. This score accurately determined which patients were at a higher risk of mortality requiring more intensive monitoring or those who could be managed on an ambulatory pathway with consequently a lower mortality risk. It however compromised of 11 parameters therefore Jiménez *et al.* calculated a simplified PESI of six parameters which is used with greater ease (12) and demonstrated a similar prognostic accuracy when compared to the PESI.

The Hestia criteria was developed by Zondag *et al.*, by conducting a prospective multicentre study in the Netherlands. This study consolidated outcomes from smaller cohort studies assessing the efficacy and safety of outpatient management of patients with low risk pulmonary embolus (13). Patients were risk stratified within 24 hours by the simple use of eleven questions and if any of the measures were found to be positive this excluded the patient from outpatient management. Of the 297 patients included in this study followed up over 3 months, there were 3 fatalities, none of which were due to fatal PEs but one was a consequence of an intracranial bleed.

The BTS earlier this year published guidelines concerning the initial outpatient management of pulmonary

embolism (14). The need for this guideline was prompted by the fact that as many as 37–44% of PEs could be managed as outpatients as well as safety concerns regarding the variability of management between centres (15).

At the ERS 2018 Congress Dr. Howard explained the BTS advisory committee recommended that clinically validated scores such Hestia criteria (13), PESI (11) and sPESI (12) were applied to risk stratify patients in the initial phase. The guidance suggested that individuals with low risk i.e., PESI I/II, sPESI of 0 and meeting the Hestia criteria should be considered for outpatient management. With the proviso that if sPESI or PESI is used to stratify the patient then a set of exclusion criteria should also be applied.

The use of anticoagulation in acute pulmonary embolus was also discussed. With the advent of direct oral anticoagulants (DOACs) if offers the clinician a non-inferior alternative to VKA with less bleeding risk (16). Some DOACs also offer a quicker time to therapeutic anticoagulation and options such as rivaroxaban (17) or apixaban (18) require no low molecular weight heparin (LMWH) bridging making it an attractive single drug regime for patients.

Clearly the choice of anticoagulation agent depends on factors including pregnancy, active malignancy, creatinine clearance, liver disease, bleeding risk factors, drug interactions as well as weight. Factor Xa inhibitors (apixaban, rivaroxaban, and edoxaban) are renally excreted.

The renal elimination rates of apixaban is 27%, rivaroxaban 33% and edoxaban around 50% (19). For this reason, such drugs are used with caution. With worsening renal function there is increased risk of bleeding with DOACs.

The International Society of Thrombosis and Haemostasis recommend that DOACs are used between a weight of 50–120 kg or a BMI less than 40 kg/m^2. It does however suggest that if using a DOAC in the super obese that peak and trough levels are measured (20).

Concerning the use of DOACs in active malignancy we are awaiting the results of randomised controlled trials comparing the standardised therapy of LMWH to DOACs (21-23). An open label study recently published in the *New England Journal of Medicine* showed non inferiority of oral edoxaban to LMWH, in cancer associated venothromboembolic (VTE) events however there was a higher bleeding rate in those on edoxaban but less recurrence of VTEs (24).

Follow-up recommendations vary amongst the studies performed. Currently the BTS suggest in the first 7 days there should be a formal review. The Hestia group arranged face-to-face consultation at 1 and 12 weeks with a telephone consultation at 6 weeks. An American study using a DOAC in the outpatient setting arranged a telephone consultation in the first 24–48 hours followed by an appointment at 6 weeks and then between 12–24 weeks (25).

Howard *et al.* currently recommend that patients should have an initially assessment during the first week of discharge after being diagnosed with a low risk acute PE. Patients should also be provided with written documentation of the signs of recurrence; major bleeding or other associated complications as well as a 24-hour point of contact at the centre.

This hot topic presented at the ERS has highlighted how the management of acute PE has changed dramatically over the years by improving patient management and consequently PE related morbidity, and mortality (26).

Non-pharmacological therapies for PH

Of those who present with acute pulmonary embolism it is widely reported that approximately 3% (27,28) of these individuals will develop chronic thromboembolic disease (CTED) or chronic thromboembolic pulmonary hypertension (CTEPH). Of these patients a proportion are able to undergo curative surgery—pulmonary endarterectomy (PEA). A recent meta-analysis reported 25% of individuals may be left with residual pulmonary hypertension (29). These patients are usually treated with standard anti-pulmonary hypertensive medications such as riociguat (only drug approved in CTEPH), phosphodiesterase (PDE) inhibitors, endothelial receptor antagonists and prostanoids.

At the ERS Congress this year the results of a prospective pilot study of a non- pharmacological treatment was discussed. It is recognised that sympathetic activity is increased in patients with PAH (30). This increase in sympathetic activity has also been shown to be a marker of a poorer prognosis (31). The rationale surrounding pulmonary artery denervation (PADN) therefore is to induce vasodilatation to significantly reduce the elevated pulmonary artery pressures as found by pre-clinical animal studies and recent clinical studies (32-35).

Hence PADN was offered to a small cohort of patients with residual PH post PEA. This study found that 12 months post PADN there was a continued statistically significant decrease in pulmonary vascular resistance. This study has demonstrated the safety and feasibility of PADN and that further larger studies are warranted into this field

to ascertain the long-term effects of PADN in post PEA patients as well as other cohorts of PAH patient.

Summary

2018 has seen important steps forward in the field of pulmonary vascular diseases. Risk stratification in both acute pulmonary embolism and PAH sees a move towards improving care by individualising patient therapy; whist the advent of interventional procedures provides a potential novel non-pharmacological technique for the treatment of PAH.

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Footnote

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References

1. D'Alonzo GE, Barst RJ, Ayres SM, et al. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. Ann Intern Med 1991;115:343-9.
2. Sandoval J, Bauerle O, Palomar A, et al. Survival in primary pulmonary hypertension. Validation of a prognostic equation. Circulation 1994;89:1733-44.
3. Humbert M, Sitbon O, Yaici A, et al. Survival in incident and prevalent cohorts of patients with pulmonary arterial hypertension. Eur Respir J 2010;36:549-55.
4. Benza RL, Miller DP, Gomberg-Maitland M, et al. Predicting Survival in Pulmonary Arterial Hypertension. Circulation. 2010. Available online: http://circ.ahajournals.org/content/122/2/164.short
5. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. Chest 2012;141:354-62.
6. Sitbon O, Benza RL, Badesch DB, et al. Validation of two predictive models for survival in pulmonary arterial hypertension. Eur Respir J 2015;46:152-64.
7. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the Diagnosis and Treatment of Pulmonary Hypertension. Rev Esp Cardiol (Engl Ed) 2016;69:177.
8. Boucly A, Weatherald J, Savale L, et al. Risk assessment, prognosis and guideline implementation in pulmonary arterial hypertension. Eur Respir J 2017;50. pii: 1700889.
9. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. Eur Respir J 2012;39:589-96.
10. Cohen AT, Agnelli G, Anderson F, et al. Venous thromboembolism (VTE) in Europe. Thromb Haemost 2007;98:756-64.
11. Aujesky D, Obrosky DS, Stone RA, et al. Derivation and Validation of a Prognostic Model for Pulmonary Embolism. Am J Respir Crit Care Med 2005;172:1041-6.
12. Jiménez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. Arch Intern Med 2010;170:1383-9.
13. Zondag W, Hiddinga BI, Crobach MJ, et al. Hestia criteria can discriminate high- from low-risk patients with pulmonary embolism. Eur Respir J 2013;41:588-592.
14. Luke SG, Steven B, Robin C, et al. British Thoracic Society Guideline for the initial outpatient management of pulmonary embolism (PE). Thorax 2018;73:ii1-29.
15. Jiménez D, Bikdeli B, Barrios D, et al. Management appropriateness and outcomes of patients with acute pulmonary embolism. Eur Respir J 2018;51. pii: 1800445.
16. Gómez-Outes A, Terleira-Fernández AI, Lecumberri R, et al. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res 2014;134:774-82.
17. Büller HR, Prins MH, Lensin AW, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97.
18. Agnelli G, Büller HR, Cohen A, et al. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. N Engl J Med 2013;369:799-808.
19. Lutz J, Jurk K, Schinzel H. Direct oral anticoagulants in patients with chronic kidney disease: patient selection and special considerations. Int J Nephrol Renovasc Dis 2017;10:135-43.
20. Martin K, Beyer-Westendorf J, Davidson BL, et al. Use of the direct oral anticoagulants in obese patients: guidance from the SSC of the ISTH. J Thromb Haemost 2016;14:1308-13.
21. Apixaban or Dalteparin in Reducing Blood Clots in Patients with Cancer Related Venous Thromboembolism. Available online: https://clinicaltrials.gov/ct2/show/

NCT02585713
22. Rivaroxaban in the Treatment of Venous Thromboembolism (VTE) in Cancer Patients. Available online: https://www.clinicaltrials.gov/ct2/show/NCT02583191
23. A Non-Interventional Study on Xarelto for Treatment of Venous Thromboembolism (VTE) and Prevention of Recurrent VTE in Patients with Active Cancer (COSIMO). Available online: https://clinicaltrials.gov/ct2/show/NCT02742623
24. Raskob GE, van Es N, Verhamme P, et al. Edoxaban for the Treatment of Cancer-Associated Venous Thromboembolism. N Engl J Med 2018;378:615-24.
25. Beam DM, Kahler ZP, Kline JA. Immediate Discharge and Home Treatment With Rivaroxaban of Low-risk Venous Thromboembolism Diagnosed in Two U.S. Emergency Departments: A One-year Preplanned Analysis. Acad Emerg Med 2015;22:788-95.
26. Jiménez D, de Miguel-Díez J, Guijarro R, et al. Trends in the Management and Outcomes of Acute Pulmonary Embolism: Analysis From the RIETE Registry. J Am Coll Cardiol 2016;67:162-70.
27. Zhang M, Wang H, Zhai Z, et al. Incidence and risk factors of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a systematic review and meta-analysis of cohort studies. J Thorac Dis 2018;10:4751-63.
28. Ende-Verhaar YM, Cannegieter SC, Vonk Noordegraaf A, et al. Incidence of chronic thromboembolic pulmonary hypertension after acute pulmonary embolism: a contemporary view of the published literature. Eur Respir J 2017;49. doi: 10.1183/13993003.01792-2016.
29. Hsieh WC, Jansa P, Huang WC, et al. Residual pulmonary hypertension after pulmonary endarterectomy: A meta-analysis. J Thorac Cardiovasc Surg 2018;156:1275-87.
30. Velez-Roa S. Increased Sympathetic Nerve Activity in Pulmonary Artery Hypertension. Circulation 2004;110:1308-12.
31. Ciarka A, Doan V, Velez-Roa S, et al. Prognostic Significance of Sympathetic Nervous System Activation in Pulmonary Arterial Hypertension. Am J Respir Crit Care Med 2010;181:1269-75.
32. Chen SL, Zhang YJ, Zhou L, et al. Percutaneous pulmonary artery denervation completely abolishes experimental pulmonary arterial hypertension in vivo. EuroIntervention 2013;9:269-76.
33. Chen SL, Zhang FF, Xu J, et al. Pulmonary Artery Denervation to Treat Pulmonary Arterial Hypertension. J Am Coll Cardiol 2013;62:1092-100.
34. Chen SL, Zhang H, Xie DJ, et al. Hemodynamic, functional, and clinical responses to pulmonary artery denervation in patients with pulmonary arterial hypertension of different causes: phase II results from the Pulmonary Artery Denervation-1 study. Circulation: Cardiovascular Interventions 2015;8:e002837.
35. Rothman AM, Arnold ND, Chang W, et al. Pulmonary artery denervation reduces pulmonary artery pressure and induces histological changes in an acute porcine model of pulmonary hypertension. Circulation: Cardiovascular Interventions 2015;8:e002569.

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