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Landmark papers in respiratory medicine

Updates in pulmonary hypertension and other pulmonary vascular diseases

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Pulmonary vascular disease (PVD) is a dynamic field that comprises of a spectrum of disorders such as pulmonary hypertension (PH), pulmonary embolism (PE) and chronic thromboembolic disease (CTED). Despite having different pathophysiologies, these disorders primarily affect the pulmonary circulation, with variable effects on pulmonary vascular resistance (PVR) and right ventricular (RV) function.

Many studies related to PVD were published during 2018, reflecting the growing evidence available from clinical trials, registries and translational studies. In addition, the sixth World Symposium in Pulmonary Hypertension (WSPH) was held in February 2018 in Nice, France, where 124 experts in PVD divided into 13 different task forces presented the most recent consensus in the study of PH.

In this article, we will provide an overview of landmark studies in PVD published during 2018. We will also review some of the most important updates from the recent WSPH.

Pulmonary hypertension

PH has traditionally been defined as a mean pulmonary arterial pressure (mPAP) of ≥25 mmHg; pre-capillary PH has been defined as mPAP ≥25 mmHg, pulmonary artery occlusion pressure (PAOP) (or "wedge" pressure) ≤15 mmHg and PVR ≥3.0 Wood units (WU) [1].

It is recognised that the normal values for mPAP are ~14.0±3.3 mmHg [2]; two standard deviations above this mean value would suggest that a mPAP >20 mmHg is higher than the upper limit of normal.

The current definition of PH uses an arbitrarily chosen cut-off of mPAP ≥25 mmHg. Whilst this definition has been broadly accepted and used in clinical trials and registries, observational studies have reported increased morbidity and mortality in different subsets of patients with a mPAP of 21–24 mmHg, such as in patients with scleroderma [3], heart failure or chronic lung disease [4], and CTED [5]. Patients with mild elevations in mPAP but below the 25-mmHg cut-off (also known as "borderline" PH) may also be more likely to develop overt PH than those with a mPAP ≤20 mmHg [3].

Consequently, one of the main recommendations of the recent sixth WSPH was to update the haemodynamic definition of PH. The proposed new definition is characterised by a mPAP >20 mmHg; as such, pre-capillary PH is defined as mPAP >20 mmHg, PAOP ≤15 mmHg and PVR ≥3 WU [6]. It should be emphasised that this elevation of PVR is an essential component of the definition, since it allows discrimination between elevations in pulmonary artery pressures due to PVD and those due to elevations of PAOP or due to high cardiac output [6]. It should also be noted that this change in the haemodynamic characterisation of PH does not suggest treating these patients but instead highlights the need for closer monitoring

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in this population. Further studies and trials are required to determine a treatment strategy in this population.

RV adaptation is considered an important determinant for survival in patients with pulmonary arterial hypertension (PAH). The symptomatology and clinical outcomes are largely determined by RV function [7]. The current guidelines for the diagnosis and treatment of PAH recommend stratifying PAH patients by using a multiparametric approach including clinical and haemodynamic data, as well as data on RV function and exercise parameters, to define low-, intermediate- and high-risk status of mortality at 1 year [1].

This risk stratification approach has proven to be effective at decreasing mortality in patients with PAH, as demonstrated by Hoeper *et al*. [8], where the 5-year survival rates were 75.9%, 51.9% and 32.4% for patients in the low-, intermediate- and high-risk categories, respectively ($p<0.001$ for all group comparisons). Furthermore, changes in risk status correlated with mortality. For example, the survival rates at 5 years were 80.6% for patients who remained in the low-risk category, as compared to 69.7% for patients who were initially considered low-risk but moved to an intermediate-risk category on follow-up [8].

This risk stratification method was reinforced in the recommendations of the sixth WSPH. Consequently, there was also emphasis on a treatment approach based on risk category rather than solely on symptomatology or functional class [9].

Pulmonary embolism

The incidence of PE has continued to increase whilst the associated mortality has been in decline over the last decade. The reported incidence rate for PE ranges from 29 to 78 per 100000 person-years [10].

An area of growing interest is the use of clinical risk scores for the assessment of PE probability. In fact, in addition to the well-known Wells and Geneva scores (and their simplified version in combination with D-dimer measurements), the Pulmonary Embolism Rule-Out Criteria (PERC) and YEARS algorithms are also frequently used.

The combination of the PERC and YEARS algorithms was associated with a lower risk of PE diagnostic failure. Furthermore, the use of these algorithms, individually or together, reduced the need for computed tomographic pulmonary angiography (CTPA) compared with the Wells or Geneva scores [11].

The guidelines for the outpatient management of pulmonary embolism published by the British Thoracic Society (BTS) were developed with the aim to standardise the management of patients with PE. Importantly, it recommended to use two different algorithms for the assessment of eligibility for outpatient treatment.

Patients with a Pulmonary Embolism Severity Index (PESI) class I or II, Simplified PESI score 0, or meeting no Hestia criteria (with no evidence of RV strain) are considered low-risk and deemed eligible for outpatient treatment of PE [12]. The Hestia criteria are patient factors that preclude outpatient therapy (*i.e.* high risk of bleeding or need for supplemental oxygen). Use of the Hestia criteria is also recommended for the assessment of outpatient management in those patients with malignancy, since the other scores automatically exclude those with cancer.

Patients with confirmed PE can be treated with a two-drug regimen that includes either dabigatran or edoxaban, with the concomitant use of a low-molecular-weight heparin (LMWH) for bridging, or a single-drug regimen with rivaroxaban or apixaban, the latter regimen being preferred due to its simplicity [12].

In patients with cancer-associated PE, most guidelines recommend LMWH for at least 3–6 months. Regarding the use of direct oral anticoagulants (DOACs), data from recent clinical trials show that edoxaban is noninferior to dalteparin in regard to the incidence of recurrent venous thromboembolism (VTE) or major bleeding [13], and that rivaroxaban has a relatively lower incidence of recurrent VTE but a higher incidence of clinically relevant nonmajor bleedings, as compared to dalteparin [14].

As such, the International Society on Thrombosis and Haemostasis guidance states that DOACs could be used in patients with a low risk of bleeding and no drug–drug interactions with current systemic therapy [15]. There are, however, ongoing randomised controlled trials of other DOACs; consequently, concise recommendations for treatment of cancer-associated PE can be expected only after publication of these clinical trials.

Chronic thromboembolic pulmonary hypertension and CTED

Chronic thromboembolic pulmonary hypertension (CTEPH) is a potentially curable form of PH.

The updated recommendations from the Cologne Consensus Conference 2018 are the latest on evaluation of patients with CTEPH and CTED [16]. It is recommended that those patients with an intermediate or high probability of PH on transthoracic echocardiography should be further investigated after ≥3 months of adequate anticoagulant therapy.

Lung ventilation/perfusion scintigraphy is the screening test of choice and a normal scan rules out CTED/CTEPH. In the case of an abnormal perfusion scan, the next step in the diagnostic algorithm includes CTPA, right heart catheterisation and selective pulmonary angiography [16].

Depending on the distribution of the disease (*i.e.* in proximal disease), the advised treatment for CTEPH is pulmonary endarterectomy (PEA) in a multidisciplinary CTEPH centre. Medical therapy and balloon pulmonary angioplasty are additional therapeutic options for patients with inoperable CTEPH [16].

CTED is characterised by similar symptoms and perfusion defects as CTEPH but without PH at rest, as defined by the sixth WSPH [17]. PEA results in haemodynamic and clinical improvements in CTED patients, as demonstrated by Guth *et al*. [18]. The selection of patients deemed eligible for PEA in the absence of PH must be made based on patients' expectations and their perioperative risk [16].

Summary

PVD is a growing field of special interest for respiratory scientists. The increasing number of available studies and development of new treatment guidelines go along with the increasing interest in this fascinating field. While areas of debate and controversy exist, there is consensus on risk stratification based on RV adaptation for the different PVD disorders. The recommendations from the sixth WSPH and the proposed new definitions for PH, as well as the new BTS guidelines for outpatient management of PE, were a few of the landmark publications during 2018.

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Conflict of interest

None declared.

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