ERS International Congress 2023: highlights from the Pulmonary Vascular Diseases Assembly

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Shareable abstract (@ERSpublications)
Key highlights in pulmonary vascular diseases from #ERSCongress 2023 include insights into disease modification in PAH and novel therapies, PH associated with lung disease, lung embolism and CTEPH https://bit.ly/476G6cT

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Abstract

Pulmonary vascular diseases such as pulmonary embolism and pulmonary hypertension are important and frequently under-recognised conditions. This article provides an overview of key highlights in pulmonary vascular diseases from the European Respiratory Society International Congress 2023. This includes insights into disease modification in pulmonary arterial hypertension and novel therapies such as sotatercept and seralutinib. Exciting developments in our understanding of the mechanisms underpinning pulmonary hypertension associated with interstitial lung disease are also explored. A comprehensive overview of the complex relationship between acute pulmonary embolism and chronic thromboembolic pulmonary hypertension (CTEPH) is provided along with our current understanding of the molecular determinants of CTEPH. The importance of multidisciplinary and holistic care cannot be understated, and this article also addresses advances beyond medication, with a special focus on exercise training and rehabilitation.

Introduction

Diseases of the pulmonary vasculature contribute considerably to the global burden of chronic respiratory diseases. Pulmonary vascular diseases encompass a spectrum of conditions that are frequently under-recognised, including pulmonary embolism (PE) and pulmonary hypertension (PH). The European Respiratory Society (ERS) has made a concerted effort to improve awareness, provide education and facilitate research into this important area [1, 2] and this was reflected in the pulmonary vascular disease track at the 2023 ERS Congress. We witnessed exciting developments in novel therapies for pulmonary

arterial hypertension (PAH) that target the transforming growth factor-β (TGF-β) and the platelet-derived growth factor receptor (PDGFR) pathways. Our understanding of the precise mechanisms underpinning PH associated with interstitial lung disease (PH-ILD) has improved and there is renewed interest in screening tools, phenotyping and new therapies for this important group. There are continued advances in the fields of venous thromboembolism and chronic thromboembolic pulmonary disease. The accurate and timely diagnosis of acute PE and the appropriate management and early identification of specific complications such as chronic thromboembolic pulmonary hypertension (CTEPH) are important areas that were explored at the ERS International Congress 2023. The pulmonary vascular diseases community had a prominent role and strong voice at the congress and the future appears bright for these important diseases [3].

Novelties in pulmonary arterial hypertension

The concept of disease modification in PAH was explored at the 2023 ERS Congress. The definition of a disease-modifying treatment is one that targets the underlying pathophysiology and results in a sustained clinical benefit, which differs from a purely symptomatic benefit. Therefore, there should be a clear correlation with clinical outcomes and a disease-specific biomarker that can demonstrate this, as presented by S. Sahay (Houston, TX, USA). Five levels of disease modification in PAH were outlined, with level 1 therapies slowing clinical decline and level 5 therapies resulting in a cure, *e.g.* lung transplantation. Among new treatments tested for PAH, two seem particularly promising and offer potential disease-modifying properties. These include sotatercept, targeting the TGF-β superfamily pathway, and seralutinib, an inhaled PDGFR inhibitor.

Sotatercept is an activin signalling inhibitor that aims to restore the balance between pro-proliferative and anti-proliferative signalling in PAH. In the phase 2 PULSAR and phase 3 STELLAR trials, both conducted in PAH patients with World Health Organization functional class II or III, sotatercept added to background double or triple combination therapy significantly improved pulmonary vascular resistance (PVR) and exercise capacity assessed by 6-min walk distance (6MWD) [4, 5]. A *post hoc* analysis of the STELLAR trial assessed changes in haemodynamic parameters and right ventricular function as assessed by right heart catheterisation (RHC) and echocardiography at 24 weeks. Relative to placebo, sotatercept led to significant improvements in haemodynamic parameters including right atrial pressure, mean pulmonary artery pressure (mPAP), mixed venous oxygen saturation and pulmonary artery elastance and compliance, as well as tricuspid annular plane systolic excursion (TAPSE) to systolic pulmonary artery pressure ratio as assessed by echocardiography. However, there were no significant changes in heart rate, cardiac output, cardiac index, stroke volume, stroke volume index or TAPSE. Together with the clinical benefits observed with sotatercept in the STELLAR trial, results of this *post hoc* analysis underscore the clinical relevance of improving cardiopulmonary haemodynamic parameters, right heart function and coupling between the pulmonary artery and the right ventricle in these patients [6].

Seralutinib is a tyrosine kinase inhibitor administered *via* a dry powder inhaler. Seralutinib inhibits PDGFR, colony-stimulating factor-1 receptor (CSF1R) and c-KIT. In addition, seralutinib leads to an increase in bone morphogenetic protein receptor 2 (BMPR2), thereby promoting antiproliferative action. The phase 2 TORREY trial met its primary end-point by demonstrating a significant reduction in PVR in patients with PAH treated with inhaled seralutinib, on background double or triple combination therapy [7]. A substudy presented at the congress used thin-section, volumetric, non-contrast chest computed tomography (CT) followed by automated pulmonary vascular segmentation to assess seralutinib-induced reverse remodelling of the pulmonary vasculature. Blood vessel volumes were determined at distinct levels defined by vessel cross-sectional area (>5 mm^2 and >10 mm^2) in 19 subjects on double or triple PAH-specific background therapy at baseline and at 24 weeks. There was a significant improvement in the ratio of blood vessel volume in distal vessels relative to larger vessels, consistent with a reverse remodelling effect of seralutinib. The change in the ratio of blood vessel volume from baseline to week 24 correlated with the change in haemodynamic parameters such as pulmonary artery compliance and stroke volume [8]. A CT substudy is planned for the phase 3 PROSERA trial to increase our understanding of the effects of seralutinib on pulmonary vascular remodelling (ClinicalTrials.gov: NCT05934526). An improved understanding of the role of the PDGF and TGF pathways in the pathobiology of PAH and the development of therapies to inhibit these pathways have raised great hopes for the future management of PAH and would not be possible without basic science. A selection of molecular pathways that were presented at the poster session for basic mechanisms in PH are outlined below in table 1.

The haemodynamic definition of PH was re-examined at the Sixth World Symposium on Pulmonary Hypertension [19], and a precapillary pattern of PH is now defined as mPAP >20 mmHg, PVR >2 WU and pulmonary artery wedge pressure (PAWP) ⩽15 mmHg [3, 20]. The demographics of PAH are changing and the clinical phenotype is evolving, and this was taken into consideration when constructing the 2022

TABLE 1 Molecular pathways that were presented at the poster session for basic mechanisms in pulmonary hypertension (PH) at the European Respiratory Society Congress 2023

Authors	Molecular pathways	Regulation	Consequences and what this study brings
PAH			
Grobs *et al.* [9]	ATP citrate lyase	Increased	ATP citrate lyase inhibition induced a decrease in proliferation and survival of PASMC, improved haemodynamic parameters and vascular remodelling in animal models
Kurakula *et al.* [10]	Histone deacetylase	Increased	Inhibition of histone deacetylase reverses vascular remodelling and improves RV function
Mirza *et al.* [11]	BMP9	BMP9 induced SEMA3G expression in pulmonary microvascular endothelial cells	BMP9 treatment of pulmonary microvascular endothelial cells increased SEMA3G expression and reduced VEGF-induced angiogenesis Sema3G might play an important role in balancing pro-angiogenic VEGF and anti-angiogenic BMP9 signalling
Lemay *et al.* [12]	DHPS and eIF5A	Increased	Targeting DHPS-mediated hypusination of eIF5A improves vascular remodelling in PAH
Lemay *et al.* [13]	FBIS	Increased	Inhibition of FBIS improved haemodynamic and vascular remodelling in animal models
Mumby *et al.* [14]	BET	Increased	Inhibition of BET using JQ1 and decreased TNF-α-driven inflammation in primary pulmonary vascular cells
Bourgeois *et al.* [15]	Histone acetyltransferase P300/CBP	Increased	Inhibition of P300/CBP diminished cardiomyocytes hypertrophy and reversed pro-proliferative and apoptotic resistant phenotype of PASMC
Schang *et al.* [16]	HS135 (a designed receptor-based fusion protein)	Synthetic fusion protein, not present in subjects	HS135 traps growth differentiation factors and improved pulmonary vasculature and gene expression profile in the monocrotaline rat model of PAH and group 2 PH
Duijvelaar *et al.* [17]	Sodium-glucose cotransporter 2	Unclear	Empagliflozin attenuated pulmonary vascular remodelling and improved haemodynamic parameters in a rat model of PAH, which could be mediated by improved mitochondrial biogenesis and reduced proliferation
RV remodelling			
Mamazhakypov *et al.* [18]	Osteopontine	Increased during right heart remodelling	While increased osteopontine has been identified as a predictor of poor prognosis, knock out of osteopontine led to worse prognosis (increased RV remodelling, increased mortality)

PAH: pulmonary arterial hypertension; RV: right ventricle; PASMC: pulmonary artery smooth muscle cell; BMP9: bone morphogenetic protein 9; SEMA3G: semaphorin 3G; VEGF: vascular endothelial growth factor; DHPS: deoxyhypusine synthase; eIF5A: eukaryotic translation initiation factor 5A; FBIS: fibronectin-binding integrins system; BET: bromodomain and extra-terminal domain; TNF-α: tumour necrosis factor-α.

European Society of Cardiology (ESC)/ERS guidelines for the diagnosis and management of PH [3, 21]. PAH is frequently identified in older patients with concomitant comorbidities and current guidelines recommend initial monotherapy for these patients, rather than upfront double combination therapy, because side-effects are more common in this cohort and therapeutic gains may be attenuated [3]. Data presented by Boucly *et al.* [22] compared the efficacy of initial oral monotherapy and double combination therapy in PAH patients with at least one cardiovascular comorbidity (obesity, diabetes, hypertension, coronary heart disease) from the French PH registry. Among 1088 patients with PAH and at least one comorbidity, 655 received initial monotherapy and 398 double combination therapy. The proportion of patients achieving a low-risk or intermediate-low-risk status was higher in patients with initial dual therapy compared to initial monotherapy (53% *versus* 45%, p=0029), with higher functional and haemodynamic improvement, and a trend to better survival at 1 year but without statistical differences in long-term mortality. The tolerability of the two strategies was similar with similar rates of discontinuation. Further data pertaining to this important topic were presented by V. McLaughlin. This was a *post hoc* study on the effects of inhaled treprostinil (iTre) on patients with PAH and one or more cardiovascular comorbidity in the pivotal TRIUMPH study. This was a randomised double-blind controlled study of iTre in patients with PAH on background therapy, and met its primary end-point of change in 6MWD. Of the 235 patients in the study, 68 had one comorbidity and 56 had two or more comorbidities. Improvement in 6MWD and N-terminal pro-brain natriuretic peptide (NT-proBNP) were similar in patients treated with iTre compared to placebo, irrespective of the number of comorbidities [23]. These studies suggest that double

combination PAH therapy and even triple therapy were well tolerated and effective in patients with PAH and cardiovascular comorbidities and underscore that further research is warranted to address this important topic.

Group 3 pulmonary hypertension

PH associated with lung diseases and/or hypoxia (group 3) is frequently recognised in patients with COPD, emphysema, ILDs, combined pulmonary fibrosis and emphysema, and hypoventilation syndromes [3]. Approximately 5–10% of patients with PH associated with chronic lung diseases (CLDs) will develop severe PH, which is defined at RHC as a PVR >5 WU as per the 2022 ESC/ERS PH guidelines [3]. To date, there are still unmet clinical needs mainly to better define a specific treatment strategy. There is limited and conflicting evidence indicating the use of approved medication for patients with group 3 PH, apart from iTre that has recently proved to be effective in patients with PH-ILD [24]. The main baseline treatment strategy for group 3 PH is the optimisation of the underlying lung disease including supplementary oxygen and noninvasive ventilation, where indicated, as well as enrolment into a pulmonary rehabilitation programme.

PH is commonly observed in patients with ILDs and has significant effects on patient outcome. Pulmonary vascular remodelling in PH-ILD was often viewed as a "passive" process that was limited to regions of fibrotic lung. There has been a paradigm shift in PH-ILD because we now appreciate that pulmonary vascular changes can occur in regions of apparently normal pulmonary parenchyma with no fibrosis. A recent review by Ruffenach *et al.* [25] describes the common and distinct lesional mechanisms observed in ILD patients with or without PH-ILD. In both cohorts, BMPR-2 expression and signalling is reduced and altered adenosine signalling is observed. The genetic signature of these cohorts differs, with increased pro-angiogenic gene expression in those with PH-ILD. Furthermore, hypoxia-inducible factor-1 activation and the Slug-prolactin-induced-protein axis are upregulated in PH-ILD, resulting in pro-proliferative and anti-apoptotic signalling [25].

While the PH-ILD physiopathological process is induced by specific underlying mechanisms, its occurrence can be challenging to identify in clinics. PH-ILD risks factors are numerous and include genetic, epigenetic and environmental factors [26]. Moreover, underlying ILD can be associated with an increased risk of PH-ILD given that it is recognised in combined pulmonary fibrosis and emphysema and lymphangioleiomyomatosis. Screening tools have been developed to identify PH-ILD but require further validation [27, 28]. A modified Delphi consensus published in 2022 highlighted important risk factors, symptoms, signs and investigation results that should prompt consideration of PH in patients with ILD [29]. These include CT features such as increased pulmonary artery to ascending aorta ratio, a decline in the diffusing capacity for carbon monoxide of >15%, or disproportionate oxygen reduction during exercise compared to ILD extension. The importance of longitudinal follow-up (trends) was emphasised, particularly worsening gas exchange and/or exercise tolerance out of proportion to the decline in lung volumes. In this context, abnormal clinical changes should prompt further investigation with echocardiography to exclude the occurrence of PH-ILD, and RHC should be considered in specific subgroups of patients [29].

It is frequently challenging to differentiate PH-CLD from other important causes of PH, including idiopathic PAH, especially when patients have mild lung disease based on imaging with preserved pulmonary function. New diagnostic tools to tackle this question are under development to try to enhance disease quantification and prediction. During the ERS Congress 2023, Dwivedi *et al.* [30] presented their study exploring the use of artificial intelligence (AI) to improve the quantification and prognostication of lung disease on CT in PH. They developed a novel deep-learning AI model to quantify the percentage of normal lung and lung with abnormalities, defined as ground glass, ground glass with reticulation, emphysema, honeycombing and fibrosis. Combining AI with clinical and radiological assessments improved prognostic predictive strength and the authors suggest that this could enhance phenotyping and patient management [30]. In a prospective study of 117 patients with CLD and 38 with idiopathic PAH, Garcia *et al.* [31] performed quantitative assessment of pulmonary vascular volumes using CT to investigate whether patients with severe PH associated with specific lung conditions had a lower density of pulmonary microvasculature. Interestingly, in this study the severity of PH-CLD was unrelated to the extent of the disease assessed through vascular volume.

The role of PH-specific therapies is still unclear and they are frequently suspected to be deleterious on gas exchange due to the inhibition of hypoxic vasoconstriction, despite the identification of specific pathways involving preserved parenchymal lung regions. A systematic review and meta-analysis of the effect of targeted PAH therapies on arterial oxygenation in patients with PH-CLD by Blanco *et al.* [32] has

addressed this specific question. This meta-analysis of 11 studies including 872 patients concluded that the use of these targeted therapies in patients with group 3 PH does not appear to impair arterial oxygenation.

Due to conflicting evidence, prescribing practices for patients with PH-ILD are heterogeneous. There are no approved specific therapies and multiple trials failed to be effective in multiple PH-ILD conditions (unless in PH-ILD). In a survey of 55 clinicians exploring the management of PH-ILD in Europe, 50% of physicians reported prescribing off-license PH therapies for their patients with PH-ILD [33]. Of these, phosphodiesterase type-5 inhibitors (PD5i) are generally considered as the first-line drug in 78% of cases. This underscores the urgent need for evidence-based guidelines and licensed therapies for this group of patients [33]. Inhaled iTre was approved for use in patients with PH-ILD by the US Food and Drug Administration in 2022 following the INCREASE trial and it is the first licensed drug in this indication [24]. The INCREASE trial was a 16-week randomised placebo-controlled trial evaluating iTre in patients with PH-ILD, which met its primary end-point of change in 6MWD [24]. In a *post hoc* analysis of the open label extension study, a cohort of 36 patients were subsequently initiated on PD5i [34]. Preliminary data indicate that the addition of PD5i in a subset of patients with PH-ILD treated with iTre may be safe. The overall field of group 3 PH is large and composed of various diseases. PH-CLD remains to be thoroughly explored to clarify the potential benefit of specific vasodilator treatments and to confirm the best strategy for patient management [34].

Pulmonary embolism and chronic thromboembolic pulmonary hypertension

The past year saw continued advances in the fields of venous thromboembolism (VTE) and chronic thromboembolic pulmonary disease. The accurate and timely diagnosis of acute PE and the appropriate management and early identification of specific complications such as CTEPH are important areas that were explored at the ERS Congress 2023.

The PEP study (Prevalence of PE in patients with an acute exacerbation of COPD) was an important multicentre cross-sectional study that aimed to define the prevalence of PE in patients admitted with COPD and an acute deterioration in respiratory symptoms [35]. This study reported a PE prevalence of 5.9% in this cohort [35]. A *post hoc* analysis of this study was presented at the 2023 ERS Congress, which explored the safety and efficacy of CT-sparing diagnostic strategies for patients admitted with acute exacerbations of COPD. The revised Geneva and Wells PE scores are widely used and validated scores that use fixed D-dimer thresholds. These were compared to CT-sparing strategies such as the ADJUST-PE (Age-adjusted D-dimer cutoff levels to rule out PE) [36], YEARS [37], PEGeD [38] and 4PEPS (4-Level PE Clinical Probability Score) [39] scores. While the CT-sparing strategies reduced the need for CT pulmonary angiogram by 32%, they were associated with a reduced safety profile and increased false negatives [40].

Another important cohort of patients that are at risk of VTE are those with active cancer. The HOME-PE randomised trial explored the use of the Hestia criteria or simplified Pulmonary Embolism Severity Index score to triage patients with acute PE for home treatment and included patients with cancer-associated thrombosis [41]. The primary outcome of this study was a composite of recurrent VTE, major bleeding and all-cause death within 30 days post-randomisation. A *post hoc* analysis of this study of patients with cancer-associated thrombosis revealed that active cancer was associated with an increased risk of the primary outcome at 30 days (OR 7.95, 95% CI 1.48–42.82); however, home treatment was not (OR 1.19, 95% CI 0.15–9.74). These data suggest that home treatment may be feasible and safe for patients with cancer-associated thrombosis and a low-risk PE profile [42].

There is immense interest in the identification of biomarkers that could identify patients at increased risk of complications post-PE. Troponin and NT-proBNP are readily available cardiac biomarkers that are frequently used to risk stratify patients at the time of acute PE. In a single-centre retrospective study of 479 patients post-acute PE, a significant rise in one of these biomarkers occurred in 34% of patients (n=163) within 72 h of acute PE and was associated with a significant increased risk of death. This underscores the utility of serial measurement of these biomarkers in clinical practice [43].

Complications following PE are not uncommon. Post-PE syndrome is a term that is used to describe the myriad of symptoms that may follow acute PE, including persistent dyspnoea, impaired exercise capacity and decreased health-related quality of life [44]. Post-PE syndrome has numerous aetiologies, which include chronic thromboembolic pulmonary disease. CTEPH is an important and frequently under-recognised complication of acute PE that is estimated to effect 2.7% of PE survivors [45]. It is characterised by persistent, organised thromboembolic material in the pulmonary vasculature and associated PH. Interestingly, not all patients with CTEPH have a history of acute PE and, similarly, not all

patients with acute PE will develop CTEPH. Furthermore, CTEPH is often misclassified as an acute PE at the time of presentation and careful consideration of clinical, echocardiographic and CT features is warranted, as they may reveal features of CTEPH [46]. For example, a systolic pulmonary artery pressure >60 mmHg on echocardiography at the time of an acute PE with two or more CT features such as organised mural thrombi, arterial bands or webs and a mosaic perfusion pattern is highly indicative of CTEPH [47]. A CTEPH checklist was presented by M. Delcroix, chair of the International CTEPH Association, which incorporates clinical features, echocardiography, CT parameters and CTEPH risk factors that should be considered at the time of acute PE and again at 3–6 months to ensure that CTEPH cases are not missed [48]. Additionally, a panel of eight plasma microRNAs that are differentially expressed between CTEPH and PE patients has been identified and could further refine risk predication models if validated in larger cohorts [49].

The molecular determinants of CTEPH have not been fully elucidated. H.J. Bogaard provided a stunning overview of the molecular steps that are potentially implicated in the pathobiology of CTEPH. These include haematological factors such as increased clot formation, reduced thrombolysis and impaired clot angiogenesis [50–52]. Infection, inflammation and endothelial injury may also play an important role in the development of CTEPH. Neutrophil extracellular traps have been observed in plasma samples from patients with CTEPH, which may lead to increased platelet aggregation [51]. Increased endothelial expression of von Willebrand factor has also been demonstrated in patients with CTEPH, and results in increased *in vitro* platelet aggregation [52]. This has been linked to an inflammatory change in NF-κB and an epigenetic change to the von Willebrand factor promoter region [52]. Altered TGF-β signalling may contribute to impaired fibrinolysis as well [50]. Pulmonary endarterectomy (PEA) material from patients with CTEPH demonstrates an inflammatory profile that may also have a role in disease progression [53]. While numerous molecular abnormalities have been described in CTEPH, the precise temporal relationship of these mechanisms is not precisely understood and requires ongoing exploration.

Vascular lesions in CTEPH are typically divided into proximal and distal disease. The former refers to proximal organised fibrous material in large pulmonary arteries and the latter describes a secondary microvasculopathy of smaller pulmonary vessels [47]. All CTEPH cases should be discussed by a CTEPH multidisciplinary team to define the distribution of disease and to guide treatment decisions. Current therapies include anticoagulation, PH-specific therapies, balloon pulmonary angioplasty (BPA) and PEA [47]. Many patients will receive a combination of these therapies, termed multimodal therapy, and while we do not currently have randomised controlled trials comparing BPA and PEA, these studies are underway.

Lifelong anticoagulation is recommended for patients with CTEPH. Preliminary results from the HEMA-HTP study (ClinicalTrials.gov: NCT02800941) were presented at the 2023 ERS Congress. This multicentre prospective study explores the frequency of major bleeding in patients prescribed oral anticoagulation therapy for CTEPH and PAH. Of the 203 patients included in the study, 23 moderate bleeds and two fatal bleeds were reported, highlighting the risk of major bleeding associated with anticoagulation use, which should not be underestimated [54]. PH therapies that are currently licensed for use in CTEPH included riociguat and treprostinil. The CTREPH study was a 24-week, randomised double-blind controlled trial of subcutaneous treprostinil in patients with inoperable CTEPH or persistent CTEPH post-PEA [55]. This study demonstrated that treatment with subcutaneous treprostinil was safe in severe CTEPH and a long-term extension of this study revealed that both high and low doses of treprostinil were efficacious [56]. BPA is an effective treatment for patients with distal CTEPH or patients who are not candidates for surgery for other reasons. It is a safe and effective treatment, particularly in centres that have accumulated experience. For patients with inoperable CTEPH and a PVR >4 WU, treatment with riociguat for 6 months prior to BPA can lower the risk of BPA-related complications [57].

PEA is a potential curative surgery for patients with proximal CTEPH and has a reliable risk profile in experienced centres. The choice of BPA *versus* PEA depends on the distribution of disease and individual patient characteristics, including comorbidities. Individualised risk assessment should be performed for all patients who are under consideration for PEA. A study by Bunclark *et al.* [58] presented at the 2023 ERS Congress highlighted the use of machine-learning tools to enhance preoperative risk assessment in patients undergoing PEA. This study identified factors that influence 90-day mortality, 5-year mortality and patient-reported outcomes post-PEA. For example, important noninvasive variables that influenced 90-day mortality included age, 6MWD and Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR) parameters [58]. Such tools could enhance individualised risk assessment and associated clinical decisions [58]. The importance of preoperative assessment of left ventricular function was also emphasised [59]. In a study of 1266 adult patients who underwent PEA between 2007 and 2018, 135 patients had an elevated postoperative PAWP. Interestingly, 60% of these patients had a normal preoperative PAWP and none of

these patients had a prior history of heart failure with preserved ejection fraction. This cohort had significantly lower postoperative gains, including pulmonary haemodynamic parameters, 6MWD, NT-proBNP and patient-reported outcomes, and impaired long-term survival. Left atrial volume and left ventricular mass were associated with an elevated postoperative PAWP, emphasising the importance of preoperative echocardiography and cardiac magnetic resonance imaging to identify these patients [59].

The choice of BPA *versus* PEA can become more complex when patients have subsegmental disease that may be anatomically suitable for both procedures. Recent surgical reports from leading CTEPH centres have demonstrated the efficacy of surgery for patients with subsegmental disease [60]. A surgical classification was described by the University of California, San Diego, to improve the description of disease within the pulmonary vasculature. This divides surgical CTEPH into proximal (I and II) and distal (III and IV) levels [61]. Meanwhile, these lesions can also be effectively treated by BPA, as demonstrated by registry data from expert centres [62]. This emphasises the importance of a CTEPH multidisciplinary team to review these complex cases and make these individualised, nuanced decisions regarding the optimum treatment approach.

It is currently unknown if CTEPH is a preventable complication of PE. The PEITHO (Pulmonary Embolism Thrombolysis) trial was a randomised comparison of thrombolysis with tenecteplase *versus* placebo for patients with intermediate high-risk PE. Long-term follow-up showed no significant difference in the incidence of CTEPH in the tenecteplase arm [63]. There is immense interest in the role of endovascular therapies such as endovascular thrombolysis and clot extraction, and studies such as the HI-PEITHO study (ClinicalTrials.gov: NCT04790370) may address this question. The aim of the above therapies for CTEPH, including PH medication, BPA and PEA, are to improve haemodynamic parameters and therefore improve patient outcomes. The natural history of CTEPH is closely tied to haemodynamic parameters, given that a mPAP >30 mmHg is associated with a 5-year survival of <50%, which falls to <10% when the mPAP is >50 mmHg [64].

Beyond medication

Exercise is an essential component of holistic care and is safe and efficacious in patients with stable PH [65]. Exercise is associated with numerous benefits, including improved quality of life, enhanced exercise capacity and a potential improvement in pulmonary haemodynamic parameters [65]. Perceived barriers to exercise and innovative ways to overcome these were addressed at the 2023 ERS Congress [66, 67]. McCormack *et al.* [67] performed a qualitative exploration of the acceptability and utility of a PH and home-based physical activity intervention. The convenience and accessibility of an exercise programme, improvement of self-regulation skills, accountability and support were identified as important themes. A fully remote exercise PH and home-based programme was considered highly acceptable among patients with PH because it facilitated exercise in a familiar setting at a convenient time and removed the burden of travel [67]. These results should influence the design of future bespoke PH exercise programmes.

Dyspnoea in patients with PH is multifactorial, and there is immense interest in the exploration of novel methods to address this and to enrich rehabilitation programmes. Vieira *et al.* [68] performed a randomised double-blind controlled trial to evaluate the impact of inspiratory muscle training (IMT) on patients with PAH and CTEPH. 13 patients with PH were randomised to IMT, which comprised 30 breaths of training with 50% of maximal inspiratory pressure, twice a day for 8 weeks. An additional 13 patients were randomised to the control group, who trained against 5 cm of water resistance. This study showed a significant improvement in 6MWD and reduced dyspnoea in patients who underwent IMT, suggesting that IMT could be an interesting add-on to existing respiratory rehabilitation if these results are confirmed in larger studies. A pilot study of a digital 1-min walk test as a novel decentralised end-point in PH research was presented by Newman *et al.* [69]. This study revealed that the 1-min walk test significantly correlated with the 6-min walk test and enhanced remote patient evaluation. It had technical accuracy, construct validity and was acceptable to patients.

Conclusion

The ERS Congress 2023 provided a wonderful opportunity to network, reconnect with colleagues and discuss the latest research in pulmonary vascular diseases with experts in the field. Emerging therapies such as sotatercept and seralutinib and novel insights into important groups such as PH-ILD and CTEPH have provided much food for thought. The publication of the 2022 ESC/ERS guidelines for the diagnosis and treatment of PH has provided a road map for future developments in the field and this is reflected in the numerous developments that were presented at the 2023 ERS Congress. The importance of sharing valuable research and education with colleagues from around the globe cannot be understated and underpins the very heart of such meetings.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: S. Cullivan reports travel grant from Janssen outside the submitted work. A. Boucly reports honoraria for lectures or travel support from AOP Orphan, Janssen, Ferrer and MSD outside the submitted work. M. Jevnikar reports travel grants from MSD, Janssen and AstraZeneca, and consulting fees from Janssen, outside the submitted work. B. Lechatier reports participation on advisory boards and travel grants from MSD and Janssen outside the submitted work. S. Ulrich receives grant money from the Swiss National Science Foundation and Swiss Lung League; and received grant money, travel fees, consultancy and for patient enrolment into trials from Janssen SA, MSD SA, Novartis SA and OrPha Swiss. L. Bertoletti reports personal fees and nonfinancial support from BMS/Pfizer, LEO-Pharma and Viatris; grants from Bayer; and grants, personal fees and nonfinancial support from MSD, outside the submitted work. O. Sitbon reports relationships with pharmaceutical companies including Merck, Janssen, Enzyvant, Gossamer Bio, Respira Therapeutics, Ferrer and AOP Orphan, outside the submitted work; relationships include grants for research and educational programmes, fees for lectures and membership of scientific advisory boards. A. Vonk-Noordegraaf reports participation on advisory boards for Ferrer, MSD and Johnson & Johnson, outside the submitted work. A. Bokan has nothing to declare. D-H. Park reports support for attending meetings and/or travel from Janssen, outside the submitted work. L. Genecand has nothing to declare. J. Guiot reports grants paid to his institution from Roche, Janssen and Merk; consulting fees from Oncoradiomics, Janssen, Boehringer Ingelheim, Pfizer and AstraZeneca; honoraria from Janssen, SMB, GSK and Chiesi; and travel support from Merck and Chiesi, all outside the submitted work. E-M. Jutant reports consulting fees from Chiesi; honoraria from Chiesi, GSK, MSD and AstraZeneca; and travel support from Janssen and MSD. L. Piccari reports grants from Janssen and Ferrer; lecture honoraria from Janssen, Ferrer, MSD and United Therapeutics; participation on advisory boards with Janssen, Ferrer and United Therapeutics; and travel support from Janssen, Ferrer and MSD, outside the submitted work. M. Lichtblau reports travel support, lecture honoraria and participation on advisory boards from Janssen, MSD and Orpha Swiss, outside the submitted work.

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