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Primer

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Pulmonary hypertension

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Abstract

Pulmonary hypertension encompasses a range of conditions directly or indirectly leading to elevated pressures within the pulmonary arteries. Five main groups of pulmonary hypertension are recognized, all defined by a mean pulmonary artery pressure of >20 mmHg: pulmonary arterial hypertension (rare), pulmonary hypertension associated with left-sided heart disease (very common), pulmonary hypertension associated with lung disease (common), pulmonary hypertension associated with pulmonary artery obstructions, usually related to thromboembolic disease (rare), and pulmonary hypertension with unclear and/or multifactorial mechanisms (rare). At least 1% of the world's population is affected, with a greater burden more likely in low-income and middle-income countries. Across all its forms, pulmonary hypertension is associated with adverse vascular remodelling with obstruction, stiffening and vasoconstriction of the pulmonary vasculature. Without proactive management this leads to hypertrophy and ultimately failure of the right ventricle, the main cause of death. In older individuals, dyspnoea is the most common symptom. Stepwise investigation precedes definitive diagnosis with right heart catheterization. Medical and surgical treatments are approved for pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension. There are emerging treatments for other forms of pulmonary hypertension; but current therapy primarily targets the underlying cause. There are still major gaps in basic, clinical and translational knowledge; thus, further research, with a focus on vulnerable populations, is needed to better characterize, detect and effectively treat all forms of pulmonary hypertension.

Sections

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Introduction

Pulmonary hypertension encompasses a multifactorial group of disorders characterized by an elevated mean pulmonary artery pressure (mPAP) of >20 mmHg, measured at rest[1,2]. A definitive diagnosis, regardless of aetiology, is made by right heart catheterization (RHC)[3]. Pulmonary hypertension can be postcapillary, as a result of an increase in pulmonary venous pressure in left-sided heart disease (LHD), or precapillary, caused by pulmonary vascular remodelling and obstruction. Remodelling of pulmonary blood vessels is characterized to varying degrees by thickening of the intimal and/or medial layer of muscular vessels and the appearance of cells expressing smooth muscle-specific markers in precapillary arterioles (distal muscularization) resulting in increased pulmonary vascular resistance (PVR). Currently, five main groups of pulmonary hypertension (Table 1) are recognized[4]. These groups reflect the multiple aetiologies (many of which can be identified by non-experts) that lead to an mPAP of >20 mmHg. Pulmonary arterial hypertension (PAH), the most recognized and studied subtype of pulmonary hypertension, is characterized by ('precapillary') pulmonary arterial remodelling[1,4]. Many under-appreciated and clinically recognized forms of pulmonary hypertension — notably those associated with LHD (LHD-PH) (group 2) and chronic lung diseases (LD-PH), such as chronic obstructive pulmonary disease (COPD), or hypoxia (group 3) — are a consequence of common cardiopulmonary disease. Pulmonary hypertension initially associated with LHD is postcapillary, whereas LD-PH and/or hypoxia are precapillary. Other less common causes of pulmonary hypertension, including group 4 pulmonary hypertension related to chronic thromboembolic disease (CTEPH) are important to recognize because they have specific therapies. Thus, pulmonary hypertension is not a single disease entity[5–7]. Furthermore, regardless of aetiology, it seems that even mild forms of pulmonary hypertension are associated with an increased risk of mortality and premature mortality[7,8].

Much of our knowledge of, and response to, pulmonary hypertension is derived from high-income countries (HICs). However, more likely there is a greater burden in low-income and middle-income countries (LMICs), where ~84% of the world population live, because of their higher prevalence of comorbidities that predispose to pulmonary hypertension[7–9] (Fig. 1). This includes uncorrected congenital heart disease (CHD), rheumatic heart disease (RHD), cardiomyopathies (CMO), chronic lung disease (notably pulmonary tuberculosis, COPD and pneumoconiosis), endemic infections (HIV, schistosomiasis), connective tissue disease and other diseases such as Takayasu arteritis and sickle cell disease[9].

Pulmonary hypertension in an insidious condition; many patients are diagnosed and are referred to a specialist heart or lung centre late in disease progression[10]. In LMICs, this problem is exacerbated by reduced access to RHC and therapeutic interventions (for example, medical therapies, interventional therapy and cardiothoracic surgery)[7,11].

Globally, there is limited information to accurately describe the epidemiology of pulmonary hypertension, especially in vulnerable populations (Box 1) and in pulmonary hypertension other than group 1. There is a need to better define the natural history, clinical course and case fatality rates for each group of pulmonary hypertension on a population basis. The Global Burden of Disease Study[12] reports on the number of disability-adjusted life-years, years of life lost due to premature mortality and years of life lived with disability attributable to pulmonary hypertension. However, source data are geographically restricted, mainly derived from hospital-based registries and rely on historically different ways to classify and identify pulmonary hypertension. Thus, the burden of disease imposed by pulmonary hypertension is probably underestimated in every region of the world[13]. This problem hampers advocacy towards prioritization of its screening, diagnosis and adequate management, particularly equitable access to potentially life-saving treatments (for example, PAH therapies) in LMICs[14].

This Primer focuses on all forms of pulmonary hypertension from a global perspective and regardless of the underlying aetiology. We describe the key features around its (known or unknown) epidemiology, natural history, pathophysiology, clinical presentation and management. Reflecting the available literature, our predominant focus is on adults with pulmonary hypertension living in HICs. However, we specifically highlight likely geographical variations in risk factors and other determinants of cardiopulmonary health that shape the true global burden of disease imposed by pulmonary hypertension. Within this framework, we also consider key issues relating to pulmonary hypertension among pregnant women (Box 2) and children.

Epidemiology

Prevalence

Generating an accurate epidemiological profile of pulmonary hypertension is difficult. This difficulty can be partly explained by the evolving definition and thresholds of pulmonary hypertension. The qualifying threshold of elevated mPAP was reduced from ≥25 mmHg to >20 mmHg in 2018 and a PVR cut-off value of ≥3 Wood units (WU) for all forms of precapillary pulmonary hypertension was (re)introduced.

Prevalence of pulmonary hypertension. Indicative of a 'more you look, the more you find' scenario, estimated cases of PAH rose from 15 to 25 per million people in equivalent hospital registries in France[15] and Scotland[16], which reported data from incident PAH between 2002 and 2003 as well as prevalence in the period between 1986 and 2001, respectively. A granular, community-based study in Central Australia estimated the prevalence at 48 per million people in a population predominantly of Aboriginal and Torres Strait Islander descent[17]. Another study in Australia found a minimum prevalence of all forms of pulmonary hypertension of 326 cases per 100,000 (ref. 18). In a population-based retrospective study in Ontario, Canada, the incidence and prevalence of adult pulmonary hypertension increased between 1993 and 2012, and group 2 and group 3 were the most common and lethal forms of pulmonary hypertension[19]. Overall, it has been estimated that at least 1% of the world's population are affected by pulmonary hypertension[20].

Prevalence of groups 1–5. In an Australian study of pulmonary hypertension prevalence, group 2 (LHD-PH) was the greatest contributor (250 cases per 100,000), followed by group 3 (LD-PH) with 37 cases per 100,000, PAH (group 1) with 15 cases per 100,000, and group 4 (pulmonary hypertension associated with pulmonary artery obstructions) and group 5 (pulmonary hypertension with unclear and/or multifactorial mechanisms) with 5–20 cases per 100,000 (ref. 18). LHD due to underlying coronary heart disease is probably the most common cause of pulmonary hypertension worldwide[4], reflecting the predominant, historical pattern of heart disease in HIC. However, this pattern is changing with rising obesity levels and/or heart failure with a preserved ejection fraction, especially among older women[21]. In LMICs where epidemiological transition towards atherosclerotic diseases of lifestyle has yet to occur, conditions such as hypertensive heart disease, CMO, RHD and chronic infectious diseases (including cardiac complications from HIV) are more likely contributors to LHD-PH[5–7]. Moreover, the burden of

Table 1 | Classification of pulmonary hypertension

Mechanisms	WHO group	Clinical definition	Possible aetiologies
PAH (vascular remodelling of pulmonary arteries)	1	Precapillary PH	Idiopathic, heritable, drug and toxin-associated, connective tissue disease, HIV infection, congenital heart disease, schistosomiasis, portal hypertension
PH associated with left-sided heart disease	2	Postcapillary PH	Left ventricular systolic/diastolic dysfunction, valvular heart disease, congenital/acquired inflow/outflow tract obstruction, cardiomyopathy
		Isolated postcapillary PH	
		Combined postcapillary and precapillary PH	
PH associated with lung disease	3	Precapillary PH	Chronic obstructive pulmonary disease, Interstitial lung disease, chronic exposure to high altitude, hypoventilation syndromes, pulmonary diseases with restrictive and obstructive pattern
PH associated with pulmonary artery obstructions	4	Precapillary PH	CTEPH, large or proximal vessel disorders, reduced compliance and luminal narrowing
PH with unclear and/or multifactorial mechanisms	5	Precapillary PH	Haematological disorders including sickle cell disease, systemic disorders including sarcoidosis, metabolic disorders, fibrosing mediastinitis, renal failure on dialysis
		Postcapillary PH	
		Isolated postcapillary PH	
		Combined postcapillary and precapillary PH	

CTEPH, chronic thromboembolic pulmonary hypertension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.

co-existing provocations to the pulmonary system (including indoor air pollution and chronic pulmonary diseases such as tuberculosis) are likely to indicate that the ratio of LHD-PH to LD-PH is very different (Supplementary Fig. 1).

Survival

Survival among adults with pulmonary hypertension depends on the age of those affected, disease severity, underlying aetiology and the availability of evidence-based treatments[22]. This is reflected in a community-based cohort of all forms of pulmonary hypertension in Australia[18]. Within that cohort, overall mean survival from first detection (by echocardiography) was 4.4 years. Those with LD-PH (group 3) and LHD-PH (group 2) had mean survival of 4.2 and 4.3 years, respectively, with all-cause mortality >50% within 5 years. Although most studies have focused on the prognostic implications with established pulmonary hypertension, data from the clinical cohort captured by the National Echo Database of Australia, suggest that across all its forms, even mildly elevated mPAP is associated with increased mortality[23]. Cohort studies[18,23,24] and a meta-analysis[25] used eRVSP measured using Doppler echocardiography of the tricuspid regurgitation jet as a proxy for mPAP. In these studies, mild (40.0–49.9 mmHg), moderate (50.0–59.9 mmHg) and severe (>60.0 mmHg) pulmonary hypertension were associated with increased mortality rates of 23.9–55.6%, 34.4–68.8% and 44.2–78.0%, respectively[23]. Importantly, data from the Australian clinical cohort revealed that when excluding those with LHD (group 2), mortality before the age of 70 years increased from 46.7% to 79.2% of all deaths among those with an eRVSP of <30.0 mmHg (normal pressures) to those with pressures indicative of severe pulmonary hypertension (eRVSP >60.0 mmHg). Moreover, patients with eRVSP levels indicative of mild pulmonary hypertension accounted for 58% and 53% of life years lost (LYL) among men and women, respectively[26]. In Ontario, Canada, a diagnosis of any form of pulmonary hypertension in a cohort of over 50,000 patients was associated with a sevenfold increase in standardized mortality compared with the age-matched and sex-matched Canadian population[19].

Insights from registry reports

Dedicated pulmonary hypertension registries provide pivotal and comparable information about the causes, comorbidities, diagnostic classification, therapeutic management and the natural course of pulmonary hypertension worldwide. A pragmatic study in Kerala, India (the PROKERALA study) included 2,003 patients with pulmonary hypertension detected by echocardiography in 50 centres (mean age 56 ± 16 years) with 1 year follow-up[27] (Table 2); 21.2% of the patients had PAH (group 1) and 59% had LHD-PH (group 2). The annual mortality rate was 4%, and the rate of rehospitalization events was 61.7%.

The Australia and New Zealand registry analysed 2,044 patients with PAH and a median age of 58 years (interquartile range (IQR) 43–69 years), female-to-male ratio 2.8:1 and 82% classified in New York Heart Association (NYHA)/WHO functional classes (FC) III–IV, which indicate symptoms causing considerable compromise of daily life[28]. The median time to diagnosis was 1.2 years (IQR 0.6–2.7 years). Age, PAH associated with CHD (group 1), obstructive sleep apnoea and peripheral vascular disease were independently associated with a diagnostic interval of ≥1 year, which was associated with decreased 5-year survival[10]. The epidemiological profile and survival of patients with idiopathic PAH (iPAH) (group 1) matched that of contemporary registries in Europe and North America, with male sex and poorer exercise capacity being predictive of mortality, whereas obesity was found to exert a protective effect[13,29].

In South Africa, among patients presenting with de novo heart disease from a large urban township, a high number of patients with pulmonary hypertension (697 of 2,505 (28%)) complicated with right heart failure (RHF) was found[9]. Women were more frequently affected than men, and compared with equivalent HIC cohorts[10,13], more patients with pulmonary hypertension had LD-PH.

The Pan-African Pulmonary Hypertension Cohort Study (PAPUCO) was performed in nine specialist centres in four African countries. The PAPUCO study explored the antecedents, characteristics, management and 6-month survival in 220 consecutive newly diagnosed patients (209 adults, 11 children) with pulmonary hypertension diagnosed using echocardiography[7]. This study revealed poor health outcomes

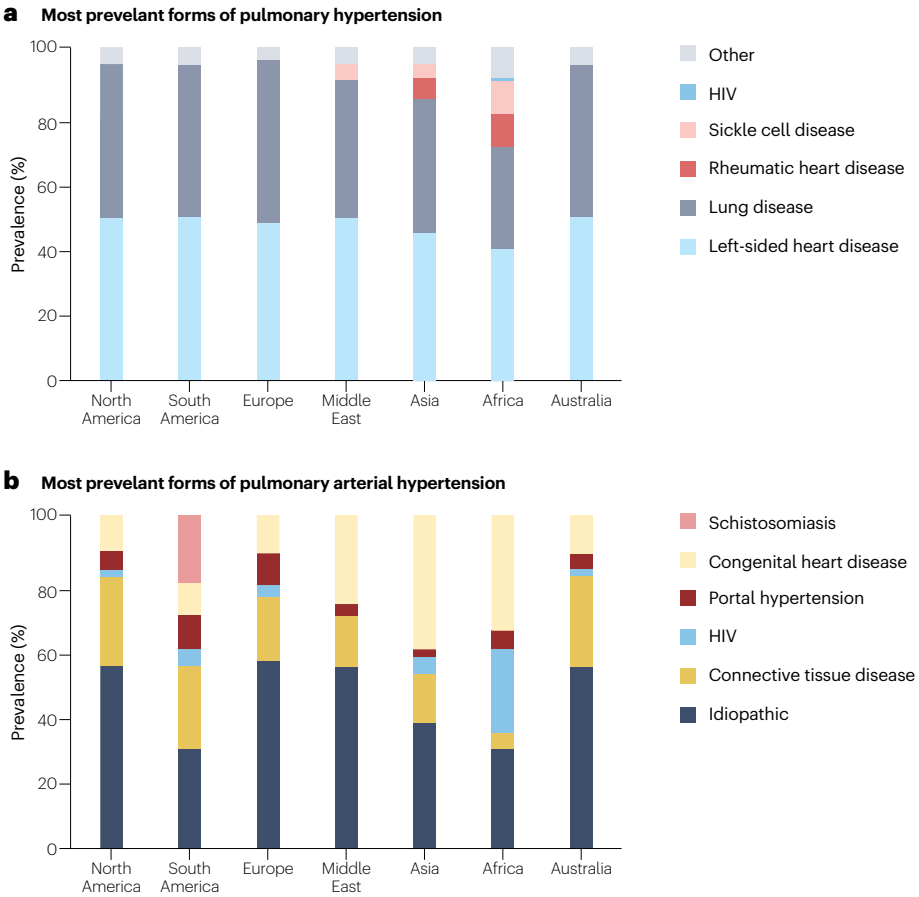


Fig. 1 | Diverse profile of pulmonary hypertension and pulmonary arterial hypertension across regions of the world. There is large diversity in the causes of pulmonary hypertension (part **a**) and pulmonary arterial hypertension (part **b**) globally, particularly in Africa and South America. Congenital heart disease and HIV represent a considerable proportion of cases in Africa, while schistosomiasis is an important cause in South America[20].

(21% mortality at 6 months) and opportunities for improving pulmonary hypertension prevention, diagnosis and management. Comparable to the findings in HIC, there was a predominance of LHD-PH (group 2; 69%), with the remainder being categorized as PAH (group 1; 16%), PH-LD (group 3; 11%), pulmonary hypertension associated with pulmonary artery obstruction/CTEPH (group 4; 2%) and pulmonary hypertension with unclear and/or multifactorial mechanisms (group 5; 2%). However, like many pragmatic registries, RHC was rarely available to definitively diagnose each case.

Paediatric pulmonary hypertension

Because they represent a large proportion of the population in LMICs with high fertility rates, children are considered special populations when addressing the optimal detection and diagnosis of pulmonary hypertension. The Paediatric Task Force of the 6th World Symposium on Pulmonary Hypertension and the 2022 ESC/ERS Pulmonary Hypertension Guidelines[1] recommended that the proposed adult definition of pulmonary hypertension be followed in paediatric pulmonary hypertension (mPAP >20 mmHg after 3 months of life) and to include a PVR index of ≥3 WU.m^2 to identify precapillary pulmonary hypertension, reinforcing the need for indexing of PVR in children. Thus, the group classification of paediatric pulmonary hypertension matches that used in adults. Critically, paediatric pulmonary hypertension is more often reversible than pulmonary hypertension in adults, and thus the benefit of early detection is greater in children.

As in the adult population, comprehensive data on the epidemiology of paediatric pulmonary hypertension are lacking, with the same biases in reporting via specialist centres and registries. The reported incidence of iPAH is lower in children than in adults. Based on different registries the incidence and prevalence of iPAH is 0.48–0.70 cases per million per annum and 2.1 and 4.4 cases per million children, respectively[30–32]. The equivalent incidence and prevalence of paediatric pulmonary hypertension specifically reported in Europe and the UK are 2.4–4.03 per million children per annum and 11.6–20.2 cases per million, respectively[30,31,33,34]. The frequency of paediatric pulmonary hypertension is likely to be higher in high-risk groups (for example, in children and adolescents with HIV and schistosomiasis). In Ontario, Canada, paediatric pulmonary hypertension accounted for 3.6% of the total pulmonary hypertension cohort of >50,000 patients identified in the provincial Institute for Clinical Evaluative Sciences (ICES) database between 1993 and 2012. Group 1 pulmonary hypertension (which includes patients with CHD) was the most common form of disease in these children (65.2%) under 16 years of age[19]. The burden of paediatric pulmonary hypertension in LMICs is likely to be much higher as pulmonary hypertension secondary to untreated CHD is more prevalent due to limited access to early diagnosis and surgical management in many regions[35].

Common causes of paediatric pulmonary hypertension include pulmonary hypertension associated with CHD, iPAH, LHD-PH and LD-PH. Importantly, postoperative pulmonary hypertension is increasingly observed in those undergoing correction of CHD in the presence of

severe PAH and elevated PVR. Cohort studies in Europe, UK and USA have all shown that most cases of paediatric pulmonary hypertension are group 1 or group 3 (refs. 30,31,33,34,36), with <10% belonging to the remaining groups. Interestingly, in a global registry published in 2012, 88% of 362 patients studied had PAH with 60–75% associated with CHD[32,34,36]. However, LD-PH (group 3) is being reported with increasing frequency among children[34,36], bronchopulmonary dysplasia and congenital diaphragmatic hernia being the major contributors. One-third of patients (31%) in a Spanish registry had pulmonary hypertension associated with multiple aetiologies, requiring a more meticulous diagnostic approach[31].

Genetic abnormalities associated with pulmonary hypertension are not uncommon (representing 25–40% of cases in various series). Down syndrome is the commonest abnormality reported[31,32,34,37]. Genes encoding members of the transforming growth factor-β/bone morphogenetic protein (TGFβ/BMP) signalling pathway have been incriminated in the pathogenesis of heritable PAH[37]. Heterozygous *BMPR2* mutations are the most common defects in this pathway, identified in >70% of individuals with familial PAH and in 10–40% of those with iPAH[31,38]. Most PAH-related mutations are inherited in an autosomal dominant fashion with incomplete penetrance, and thus families of children with iPAH or heritable PAH should be offered genetic counselling and testing[39].

From the perspectives of age and sex, children with LD-PH (group 3) tend to be younger than those presenting with PAH[34,36,40]. Overall, the distribution of pulmonary hypertension seems equal between the sexes. Female predominance (60–65%) is observed among individuals with iPAH or heritable PAH[36,40], but more so among those above 12 years of age[34]. Male predominance has been reported among individuals with LD-PH[36].

Among children with pulmonary hypertension, the rates of morbidity and survival vary depending on age, severity of pulmonary hypertension, underlying aetiology and response to treatment. The common causes of death include RHF and arrhythmias. Overall, pulmonary hypertension-targeted therapies have improved prognosis significantly in paediatric patients[32,40,41]. Transplant-free survival has been reported to vary from 86–92% at 1 year, through 74–84% at 5 years, to 69% at 10 years[34,36]. Overall survival does not appear to differ significantly between patients presenting with PAH and those presenting with LD-PH in large studies[34,36]. However, within group 1 PAH, survival for PAH associated with CHD is better than for iPAH or heritable PAH, and the highest mortality is observed among the relatively few patients with LHD-PH[34,36]. Regardless of aetiology, younger age (<2 years), advanced FC, high right atrial pressure and lower mixed venous saturation are associated with higher risk of mortality[30,31].

Pathophysiology

All forms of pulmonary hypertension share a common pathway to progressive right ventricle (RV) dysfunction and failure when elevated mPAP is left undetected and untreated. However, as a heterogeneous condition encompassing multiple pathological pathways, it is beyond the scope of this paper to describe all the specific mechanisms in disease progression relating to each specific form of pulmonary hypertension. Thus, this section provides selective pathological insights into mechanisms in pulmonary hypertension and progressive right ventricular failure (RVF) based largely on studies of group 1 pulmonary hypertension. Major knowledge gaps persist in our understanding of the pathological mechanisms underlying many more common forms of pulmonary hypertension.

There is mechanistic heterogeneity among the five pulmonary hypertension groups; however, all pulmonary hypertension is associated with adverse pulmonary vascular remodelling and progression

Box 1

Pulmonary hypertension in vulnerable and diverse populations

The early forms of pulmonary hypertension and consequent right heart failure[9,20] among young individuals living in low-income and middle-income countries (LMICs) reflect the interplay of poverty, environmental risks, uncontrolled infections, lifestyle habits and resource-poor health care[5,7] (Fig. 1). Poverty-related conditions such as endomyocardial fibrosis[216], untreated congenital heart disease and chronic exposure to indoor air pollution are important contributors[20], and coexist with increasing rates of smoking, obesity and poorly controlled hypertension. Low health literacy and minimal primary health-care services further exacerbate these factors, generating unique pathways to pulmonary hypertension in LMICs.

Schistosomiasis is a major cause of pulmonary arterial hypertension worldwide[218]. In highly endemic areas, the burden of schistosomiasis is comparable to that of tuberculosis, at around 1.9 million disability-adjusted life-years[219,220]. Around 0.5% of people living with HIV develop pulmonary hypertension during their lifetime through left ventricular dysfunction and severe lung infections[221]. Worldwide, survivors of tuberculosis are estimated at 155 million[222], some having lung destruction and fibrosis and cor pulmonale. Pulmonary hypertension is positively associated with the number of tuberculosis episodes (with the odds of pulmonary hypertension after tuberculosis being 2.13-fold (95% CI 1.17–3.88; P=0.013))[223], and previous tuberculosis increases the risk of mortality[224]. Co-pathogenic mechanisms related to inherent synergism between schistosomiasis, tuberculosis and HIV infection must be considered due to the occurrence of multiple infections[225,226].

The paucity of data from LMICs suggests that the current burden and future threat of pulmonary hypertension remains underappreciated. Pragmatic approaches to diagnosis and surveillance are required due to low access to right heart catheterization[6,7]. Gender disparities[227] and differences in survival in HIV-associated pulmonary hypertension[228] in Africa emphasize the need to understand the mechanistic intersections in multimorbidity, and to promote diversity in clinical trials by including under-represented ethnicities and racial groups in the pipelines for the development of novel pulmonary hypertension therapies[229]. Equitable access to timely diagnosis and to existing or emerging therapies should be a key priority for the global pulmonary hypertension community

Box 2

Pulmonary hypertension in pregnant women

Pregnancy is a sensitive topic in women with pulmonary hypertension, often requiring empathic communication and psychological support. Pregnancy in women with pulmonary hypertension occurs commonly in low-income and middle-income countries (LMICs) due to poor access to health care and low health literacy. Women with pulmonary hypertension have maternal mortality rates of 25–56%[230,231]; pregnancy is, therefore, contraindicated and planned termination may be indicated. Advice on contraception, screening before pregnancy and risk stratification remain paramount in women of reproductive age with pulmonary hypertension, and those who are pregnant need personalized management by experienced multidisciplinary teams[232,233]. In LMICs, the rates of preterm delivery (85–100%), fetal growth restriction (3–33%) and fetal or neonatal loss (7–13%) are particularly high[230], despite improvement in fetomaternal outcomes among women with moderate-to-severe pulmonary hypertension over the past few decades[232].

The European Registry on Pregnancy and Cardiac Disease[234] enrolled 151 women (mean age 29.2±5.6 years, 37% nulliparous and an estimated right ventricular systolic pressure (eRVSP) of >50 mmHg in 41.4%); 26% had pulmonary arterial hypertension (PAH) and 74% had pulmonary hypertension associated with left-sided heart disease[235]. Three-quarters were diagnosed before pregnancy. Maternal death up to 6 months was 5.9%. During pregnancy, 27% developed heart failure, 23.9% had emergency caesarean section and therapeutic abortion was performed in 4.0%. Data derived from a systematic review and meta-analysis of 610 pregnancies revealed maternal mortality of 11.5% (95% CI 7.6–17.2%) and pregnancy loss of 22.8% (95% CI 16.2–31.1%)[232]. Prematurity was found in seven studies and intrauterine growth restriction and/or babies below the tenth percentile for gestational age in eight studies. The pooled estimates were 51.7% for prematurity and 29.3% for intrauterine growth restriction/small for gestational age babies. The pooled estimates of caesarean delivery and general anaesthesia were 72.1% (95% CI 60.6–81.93%) and 40.1% (95% CI 26.4–55.5%), respectively[232].

Among PAH-specific drugs, the use of inhaled or intravenous prostacyclins, phosphodiesterase inhibitors and calcium channel blockers (in patients with preserved vasoreactivity) is acceptable during pregnancy, whereas endothelin receptor antagonists and riociguat are contraindicated[236].

to RVF. While knowledge gaps persist in defining mechanisms underlying the commonest forms of pulmonary hypertension (groups 2 and 3), there are lessons to be learned from the pathophysiology of the orphan disease, group 1 pulmonary hypertension (PAH). Advancing our understanding of mechanisms of disease underlying pulmonary hypertension of groups 2–5 may be particularly beneficial in managing pulmonary hypertension in vulnerable groups, particularly those living in LMICs, in whom these forms of disease predominate.

Pulmonary arterial hypertension

PAH is a pulmonary vasculopathy characterized by vascular stiffening, inflammation, vasoconstriction and loss of cross-sectional area of the pulmonary circulation. This vasculopathy involves all pulmonary artery cell types and lung immune cells, and ultimately leads to RV hypertrophy (RVH) and failure of the RV (Fig. 2). Drivers of PAH include gene mutations, activated transcription factors, dysregulated epigenetic pathways, drugs and toxins. These drivers trigger molecular mechanisms (disorders of endothelial function, mitochondrial metabolism and dynamics, ion channels, inflammation, fibrosis and adrenergic signalling) that create the hallmark features of PAH.

Endothelial damage occurs early in PAH; however, in established disease, pulmonary artery endothelial cells (PAECs), smooth muscle cells (PASMCs) and fibroblasts (PAfibs) all display a hyperproliferative, apoptosis-resistant phenotype[42,43] that is considered 'pseudoneoplastic' because of the similar abnormalities in molecular signalling pathways to those seen in cancer cells[44–47]. Transcriptomics of human PAH lungs has revealed upregulation of oncogenes and downregulation of genes encoding voltage-gated potassium channels (Kv) and mediators of apoptosis and mitochondrial metabolism[44]. Although advances in understanding the pathobiology of PAH have led to the identification of many promising therapeutic targets, PAH therapies currently only target PAEC dysfunction and vasoconstriction (for example, impaired nitric oxide bioavailability, soluble guanylate cyclase (sGC) dysfunction, reduced vasodilatory prostaglandins and increased endothelin 1)[48]. Thus, there is opportunity to translate basic science knowledge into novel therapies.

Preclinical research utilizes rat PAH models created by injection of monocrotaline (a plant-derived alkaloid) or SU5416 (a vascular endothelial growth factor 2 (VEGF2) receptor inhibitor) plus hypoxia (SU/CH). Both models recapitulate many aspects of PAH pathophysiology[49]; however, monocrotaline induces more inflammation and RVF, while SU/CH better recapitulates human PAH histology. Transcriptomics of RVs in monocrotaline-induced PAH reveals the molecular phenotype of PAH, which includes impaired mitochondrial biogenesis, increased oxidative stress and autonomic activation and upregulation of profibrotic mediators, such as periostin and LTBP2 (ref. 50), an extracellular matrix protein that is also upregulated in decompensated RVs in human PAH[51].

Genetics. Mutations in PH genes increase cell proliferation, inflammation and vasoconstriction, and/or reduce apoptosis (Fig. 2 and Box 3). Mutations occur in ~70% of people with familial PAH versus ~20% of adults and 36% of children with iPAH[52]. In paediatric PAH ~15% of mutations occur de novo[3]. *BMPR2*, the first known PAH gene[53,54], remains the most prevalent of ~20 PAH-related genes[55], accounting for ~70% of all mutated genes. Most PAH is inherited by an autosomal dominant mechanism with variable penetrance, except for autosomal recessive inheritance of *EIF2AK4*, which causes pulmonary veno-occlusive disease[56]. *BMPR2* mutation carriers have a considerable risk of developing incident PAH ranging from 0.99% per year in men to 3.5% per year in women, justifying annual screening echocardiography in individuals at risk[57]. Genetic counselling and screening are recommended because they allow early diagnosis, therapy and family planning, and have

prognostic implications[55]. Therapies are emerging that target pathways disordered by gene mutations. For example, impaired *BMPR2* signalling activates the TGFβ pathway, increasing expression of activin receptor type IIA and its ligands. Sotatercept, a soluble TGF ligand trap, targets this pathway and is beneficial in patients with PAH[58]. Success of this therapy also provides evidence of the benefit of attacking the pseudoneoplastic phenotype of PAH.

Epigenetics. Several epigenetic mechanisms, which alter gene expression without changing the DNA sequence[59], promote PAH, including dysregulation of DNA methylation, expression of microRNAs (miRs) and long non-coding RNAs and histone deacetylation[43,60–63]. DNA methyltransferases (DNMTs) methylate CpG islands in promoter regions, reducing gene transcription. DNMT activity is increased in experimental PAH, contributing to redox-mediated hypoxia-inducible factor 1α (HIF1α) activation and disease progression[64]. Conversely, TET2 reverses DNA demethylation, increasing gene transcription[65]. CHIP mutations in *TET2* promote PAH in patients[65] and lead to panchromosomal hypermethylation[66].

miRs negatively regulate mRNA stability, downregulating target proteins. Epigenetic and transcriptional regulatory pathways are interconnected in PAH. For example, decreased miR-124 upregulates nuclear factor of activated T cells (NFAT)[67,68], which decreases expression of the potassium channel Kv1.5 in PASMCs, thereby inducing vasoconstriction, proliferation, and apoptosis resistance[68,69]; conversely, restoring Kv1.5 channel expression or inhibiting NFAT regresses PAH[68]. miRs are also useful PAH biomarkers and potential therapeutics (for example, miR-130 and miR-483)[70,71].

mRNA stability is also regulated by N^6-methyladenosine (m^6A) modification. Expression of the m^6A reader, YTHDF1, and writer, METTL3, are increased in PAH[72,73] and m^6A species are increased in pathways regulating inflammation, glycolysis and PDGF signalling, and decreased in TGFβ pathways[74].

Increased histone deacetylase activity upregulates the apoptosis inhibitor, survivin[75], which contributes to the cancer-like pathophysiology of PAH[76] and reduces superoxide dismutase (SOD) expression in iPAH, increasing PAH PASMC proliferation[77].

Abnormal mitochondrial metabolism and dynamics. In PAH, glycolysis is partially uncoupled from glucose oxidation (GO) in most cardiopulmonary tissues[48,78,79]. First described in cancer, this 'Warburg metabolic shift', increases cell proliferation and impairs apoptosis in PASMCs, PAECs, PAfibs and RV fibroblasts[48]. In RV cardiomyocytes, uncoupled glycolysis impairs bioenergetics, reduces contractility, and promotes RVH and RV fibrosis[48,50]. A compensatory increase in glucose flux maintains energy homeostasis despite reduced GO[80], and can be detected in the lung and RV by ^{18}F-fluorodeoxyglucose PET[80–82]. This increase in intracellular glucose increases posttranslational O-GlcNAcylation of proteins, which contributes to RVF[83].

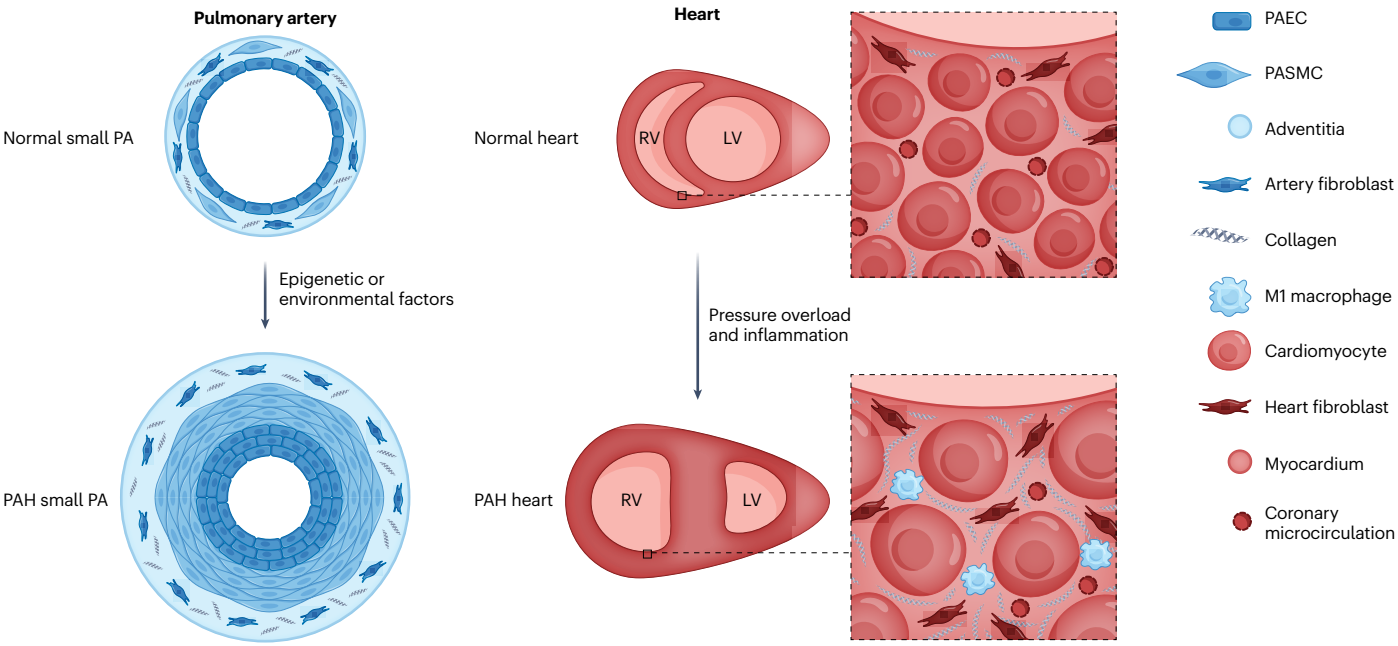
Warburg metabolism is initiated by upregulation of pyruvate dehydrogenase kinases (PDKs), triggered by epigenetic activation of transcription factors (notably HIF1α[64] and FOXO1 (ref. 84)). DNA methylation of the promoter of mitochondrial SOD2 decreases SOD2 expression, altering the redox milieu and activating HIF1α[64]. In PAH, HIF1α is further stabilized by decreased activity of prolyl hydroxylase domain (PHD), which mark HIF for proteasomal degradation[85]. Downregulation of PDH2 activates HIF2α, which reduces caveolin 1 expression and precipitates peroxynitrite-mediated nitrative stress and PAH in mice[86]. PDKs phosphorylate and inhibit pyruvate dehydrogenase (PDH), impairing GO. The translational relevance of this metabolic pathway is demonstrated by the finding that a PDK inhibitor, dichloroacetate, improves PAH in patients in whom PDH is inhibited[87].

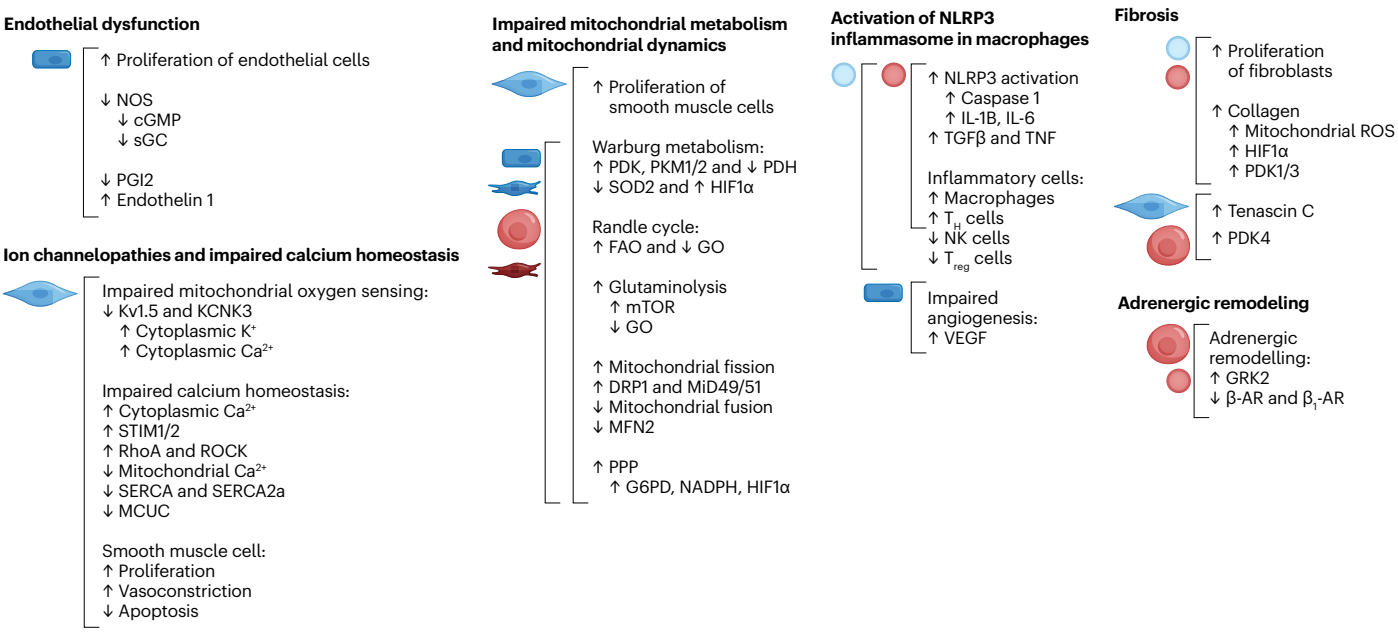
Warburg metabolism can also be initiated by increased expression of the proglycolytic M2 isoform of the terminal glycolytic enzyme, pyruvate kinase muscle isoform 2 (PKM2). In PAH PAECs, PASMCs and PAfibs, reduced miR-124 levels increase expression of polypyrimidine tract binding protein 1, a gene-splicing regulator, favouring PKM2 (refs. 88,89). Augmenting miR-124 or inhibiting PKM2 restores GO and reverses the PAH phenotype[88,89].

Table 2 | Characteristics of the population and main findings of the two published registries of pulmonary hypertension detected by echocardiography in low-income countries

	PAPUCO[7]	PROKERALA[27]
Sites	Nine specialist centres in Africa, Cameroon, Mozambique, Nigeria and South Africa	Multicentre study in India (50 hospitals)
Participants	209 adults (median age 48 years (IQR 35–64 years)), including 11 children (age range 1–17 years)	2,003 adults (mean age 56±16.1 years; no children included)
Clinical features	66% WHO functional class III–IV	65% WHO functional class II
	Median 6-min walk test distance of 252 m (IQR 120–350 m)	NA
	Median right ventricular systolic pressure 58 mmHg (IQR 49–74 mmHg)	Mean right ventricular systolic pressure 68.2 mmHg (s.d. 17.9 mmHg)
Classification/main causes	16% PAH	15.8% PAH
	69% PH due to left-sided heart disease	64.6% PH due to left-sided heart disease
	11% PH due to lung disease and/or hypoxia	14.6% PH due to lung disease and/or hypoxia
	2% chronic thromboembolic PH	3.6% chronic thromboembolic PH
	2% PH with unclear multifactorial mechanism	1.4% PH with unclear multifactorial mechanism
Prognosis	At 6 months 21% of adults with follow-up data had died	At 12 months, 4.1% had died and 1,235 (61.7%) were rehospitalized

IQR, interquartile range; NA, not available; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension.





Fatty acid oxidation (FAO) generates more ATP than GO, but requires more oxygen per ATP than GO, which may be maladaptive in ischaemic RVs. To increase GO one can exploit the Randle cycle, the reciprocal relationship between GO and FAO[90,91]. Partial FAO inhibitors, trimetazidine and ranolazine, approved heart failure and coronary artery disease therapeutics, increase GO and regress RVH in experimental[91] and human PAH[92]. FAO-related genes are upregulated in PAH, and inhibiting or deleting carnitine palmitoyltransferase 1 reduces PAH severity in SU/CH mice and mice with *Schistosoma mansoni*-induced pulmonary hypertension[93]. While many reports note increased FAO, there are also compelling reports of impaired FAO in RV cardiomyocytes manifesting as cardiac steatosis and causing lipotoxicity[94]. It is likely that dysregulation of FAO (increased versus decreased) varies between individuals and between PAH subtypes.

De novo glutaminolysis occurs in the RV in PAH and suppresses GO, promoting RVF; conversely, inhibiting glutaminolysis activates PDH and regresses monocrotaline-induced PAH, improving RV function[95]. In rapidly proliferating cells, glutaminolysis fuels anaplerosis and

Fig. 2 | Molecular mechanisms in pulmonary arterial hypertension. The top part identifies the histological and anatomical changes in the pulmonary arteries (PAs) and right ventricle that occur in PA hypertension (PAH), notably adverse pulmonary vascular remodelling and dilatation and hypokinesis of the right ventricle (RV). The drivers that promote these changes are noted. The pulmonary vascular remodelling is characterized by loss of cross-sectional area of the pulmonary vascular lumen, vascular stiffening and, in some patients, vasoconstriction. Vascular obstruction and stiffening increase RV afterload, which leads to RV hypertrophy, which is initially compensatory. However, ultimately, the RV becomes inflamed, ischaemic, dilated and fibrotic, and RV failure ensues. These anatomical features clinically manifest in exertional dyspnoea, impaired exercise tolerance, peripheral oedema and syncope. Key disease-relevant cells in PAH are shown at the top right. The cell symbols are colour-coded to identify the cells in which the numerous mechanisms in PAH, shown in the lower half of the figure, occur. The drivers of PAH that lead to these molecular signalling abnormalities include mutations in PA-related genes, activation of transcription factors (such as nuclear factor of activated T cells (NFAT), hypoxia-inducible factor 1α (HIF1α), hypoxia-inducible factor 2α (HIF2α), STAT3 and ERK1/2) and dysregulation of epigenetic factors (including DNA methyltransferases, Tet methylcytosine dioxygenase 2, microRNAs, long non-coding RNAs and histone deacetylases) and environmental factors (such as ingestion of anorexigens and amphetamines). These mechanisms, in aggregate, result in the hallmarks of PAH, which include pulmonary vascular remodelling and stiffening, increased proliferation and impaired apoptosis of pulmonary vascular cells, PA vasoconstriction, dysregulated angiogenesis, increased inflammation (in the lung and RV), increased fibrosis (in the lung and RV), and changes in the RV including capillary rarefaction, macrovascular ischaemia, reduced contractile reserve, and related RV hypertrophy and RV dilatation and hypokinesis. β-AR, β-adrenergic receptor; β_1-AR, β_1-adrenergic receptor; cGMP, cyclic GMP; DRP1, dynamin-related protein 1; FAO, fatty acid oxidation; G6PD, glucose-6-phosphate dehydrogenase; GO, glucose oxidation; GRK2, G protein-coupled receptor kinase 2; LV, left ventricle; MCUC, mitochondrial calcium uniporter complex; MFN2, mitofusin 2; MiD49/51, mitochondrial dynamics proteins of 49 kDa and 51 kDa; mTOR, mammalian target of rapamycin; NK, natural killer; NLRP3, NOD-, LRR- and pyrin domain-containing 3; NOS, nitric oxide synthase; PAEC, pulmonary arterial endothelial cell; PASMC, pulmonary arterial smooth muscle cell; PDH, pyruvate dehydrogenase; PDK, pyruvate dehydrogenase kinase; PKM1/2, pyruvate kinase muscle isoform 1/2; PPP, pentose phosphate pathway; RhoA, Ras homologue family member A; ROCK, Rho kinase; ROS, reactive oxygen species; SERCA, sarcoendoplasmic reticulum calcium ATPase; sGC, soluble guanylate cyclase; SOD2, superoxide dismutase 2; STIM, stromal interaction molecule; TGFβ, transforming growth factor-β; T_H cell, T helper cell; TNF, tumour necrosis factor; T_{reg} cell, regulatory T cell; VEGF, vascular endothelial growth factor. Adapted from images courtesy of N. Breault and I. Emon.

sustains cell proliferation[96]. Increased glutaminolysis in PAfibs stiffens the extracellular matrix via mTOR activation and hydroxylation of collagen prolines[97,98]. Increased glutaminolysis also promotes endothelial dysfunction, while a glutaminase inhibitor inhibits PAEC proliferation ex vivo and regresses monocrotaline-induced PAH in vivo[97].

Mitochondrial division (fission) and union (fusion) regulate cell proliferation and apoptosis. These mitochondrial dynamics are disordered in PAH[99], with upregulated fission and downregulated fusion. Mitochondrial fission accompanies nuclear division while mitochondrial fusion suppresses cell proliferation and promotes oxidative metabolism[99]. Increased mitochondrial fission, mediated by upregulation/activation of dynamin-related protein 1 (DRP1)[100] and DRP1 binding partners, MiD49 and MiD51 (ref. 43), permits accelerated mitosis in PAH PASMCs[100] and cancer cells[101]. Coordination of mitochondrial and nuclear division is obligatory, and inhibiting fission or enhancing fusion causes cell cycle arrest and apoptosis, and regresses experimental PAH[100,102]. Mitochondrial metabolism and dynamics offer many potential therapeutic targets in PAH.

Inflammation. In PAH, circulating cytokines, including IL-6 and IL-1β, are elevated[65]. Autoimmunity is also common in PAH, particularly in scleroderma-associated PAH. Patients with scleroderma-associated PAH have increased incidence of antibodies targeting endothelin receptor A and angiotensin receptor type 1, which predict adverse outcomes[103]. In PAH, there is an increase in T helper cells, which secrete pro-inflammatory factors promoting adverse pulmonary vascular remodelling[104]; conversely, there is a deficiency in regulatory T (T_{reg}) cells, which ameliorate pulmonary hypertension by transcriptional reprogramming[105] and by secreting cytokines and chemokines, such as IL-10 and CXCL12–CXCR4, which indirectly suppress inflammation. T_{reg} cells are also dysfunctional in PAH and fail to prevent inflammation and autoimmunity[106]. Administration of T_{reg} cells can prevent experimental PAH[106]. Macrophages are increased in the lungs and RVs in PAH and secrete inflammatory cytokines and growth factors[107]. In the lung, PAH macrophages secrete leukotriene B4, leading to PAEC apoptosis and PASMC proliferation; conversely, blocking leukotriene A4 hydrolase regresses PAH in the SU/HX rat model[108]. Natural killer cells are decreased in the lungs in PAH, suggesting a role for impaired innate immunity in pulmonary hypertension[109].

There is also right ventricular inflammation in PAH with activation of the NLRP3 inflammasome in RV macrophages[107]. NLRP3 activates caspase 1, cleaving and activating IL-1β, leading to fibrosis and inflammatory damage. The NLRP3 inhibitor MCC950 reduces RV inflammation and regresses pulmonary vascular disease in monocrotaline-induced PAH, thereby improving haemodynamics[107]. SC-144, a gp130 inhibitor, which inhibits IL-6 and STAT3 signalling, attenuates influx of inflammatory monocytes into the RV and preserves RV function, but does so without regressing adverse pulmonary artery remodelling[107]. Thus, cellular and humoral inflammation are therapeutic targets in PAH.

Potassium channelopathies. The autoregulatory mechanism in the lung for optimizing oxygen uptake, hypoxic pulmonary vasoconstriction, is mediated by a mitochondrial oxygen sensor, which regulates oxygen-sensitive Kv channels[110]. Kv channel closure depolarizes PASMCs[111], activating large-conductance voltage-dependent calcium channels (Ca_L), and increasing cytosolic calcium concentration ($[Ca^{2+}]_i$)[112–115]. Oxygen-sensing and Kv channel expression are downregulated in PAH[46,115–118]. The resulting rise in $[Ca^{2+}]_i$ and intracellular K^+ leads to vasoconstriction and apoptosis resistance, respectively[119,120]. Mutations in *KCNK3*, which encodes twin-pore acid-sensitive potassium channels, cause heritable PAH[118], underscoring the importance of K^+ channelopathies.

Calcium homeostasis. Calcium enters PASMCs via Ca_L channels and store-operated calcium channels (SOCCs). Elevated $[Ca^{2+}]_i$ in PAH PASMCs stimulates cell contraction and proliferation. Kv channel downregulation causes membrane depolarization and increases Ca_L channel opening[111], which contributes to calcium overload in PAH[46]. Ca_L channels are inhibited by dihydropyridine calcium channel blockers (for example, nifedipine). In the ~10% of patients with PAH with robust acute vasodilator responses, these drugs are therapeutic[121,122].

Box 3

Pulmonary arterial hypertension-associated genetic mutations to be considered in screening

BMP/TGFβ family
ACVRL1: activin A receptor type II-like 1
BMP10: bone morphogenetic protein 10
BMPR1B: bone morphogenetic protein receptor type 1B
BMPR2: bone morphogenetic protein receptor type 2
CAV1: caveolin 1
ENG: endoglin
GDF2: growth differentiation factor 2
SMAD1: mothers against decapentaplegic homologue 1
SMAD4: mothers against decapentaplegic homologue 4
SMAD9: mothers against decapentaplegic homologue 9

Ion channels and transporters
ABCC8: ATP-binding cassette subfamily C member 8
ATP13A3: ATPase 13A3
AQP1: aquaporin 1
KCNA5: potassium voltage-gated channel subfamily A member 5
KCNK3: potassium twin-pore domain channel subfamily K member 3

Transcription factors
SOX17: SRY box 17
TBX4: T-box transcription factor 4
KLF4: Krüppel-like factor 4

Miscellaneous
FBLN2: fibulin 2
KDR: kinase insert domain receptor
PDGFD: platelet-derived growth factor D
PTGIS: prostaglandin I2 synthase
RNF213: ring finger protein 213
TET2: Tet methylcytosine dioxygenase 2
EIF2AK4: eukaryotic translation initiation factor 2 alpha kinase 4 (mutations in *EIF2AK4* are inherited in an autosomal recessive manner and are linked to pulmonary veno-occlusive disease)

T-type calcium channels may also contribute to cell hyperproliferation and apoptosis resistance in iPAH PASMCs[123].

Calcium levels in the endoplasmic reticulum reflect uptake by sarcoendoplasmic reticulum calcium ATPase (SERCA) and release by inositol-1,4,5-triphosphate receptors. When intracellular calcium stores are depleted, SOCC entry occurs via a stromal interacting protein (STIM1/2)-dependent mechanism. SOCC entry and the expression of the calcium sensors, STIM1 and STIM2, are increased in PAH[124]. STIM2 is upregulated in iPAH PASMCs and increases $[Ca^{2+}]_i$, thereby activating proliferation and inhibiting apoptosis[125]. SERCA2a is downregulated in PAH PASMCs and SERCA2a gene therapy regresses monocrotaline-induced PAH[126].

Intramitochondrial calcium concentration ($[Ca^{2+}]_{mito}$) is decreased in PAH PASMCs due to impaired function of the mitochondrial calcium uniporter complex (MCUC), an ion channel that allows calcium into the mitochondrial matrix[127]. Decreased MCUC expression is driven by elevated miR-138 and miR-25 expression[128]. Loss of MCUC function increases $[Ca^{2+}]_i$, promoting mitochondrial fission and vasoconstriction, while reducing $[Ca^{2+}]_{mito}$, which inhibits oxidative metabolism by inhibiting calcium-dependent metabolic enzymes[129]. Restoring MCUC function reduces fission, increases GO and regresses PAH[128]. The function of the MCUC seems to link metabolism and mitochondrial dynamics in PAH.

In PAH, RhoA and its target ROCK are activated by vasoconstrictors, such as endothelin 1 (ref. 130). ROCK sustains vasoconstriction by inactivating myosin light chain phosphatase, thereby increasing myosin contractility. ROCK-mediated vasoconstriction is resistant to Ca_L blockers; however, the ROCK inhibitor, fasudil, reverses vasoconstriction and improves RVF in patients with pulmonary hypertension[131]. While we already use Ca_L blockers to treat PAH in limited patient subsets, there is an unexploited opportunity to modulate intracellular calcium handling and mitochondrial calcium flux as therapeutic targets.

Adrenergic remodelling. In PAH, circulating noradrenaline levels are high[132] and RV inotropic reserve is diminished, reflecting downregulation and desensitization of α_1-adrenergic receptors (α_1-ARs) and β_1-ARs by increased G protein-coupled receptor kinase 2 (GRK2)[133]. GRK2 phosphorylates agonist-bound β-ARs, engaging β-arrestin and promoting receptor internalization and degradation[133]. GRK2 also reduces coupling of β_1-ARs to adenylyl cyclase and impairs cAMP production by inotropes, thereby reducing their inotropic effects. In PAH-associated RVF, β-AR density, tissue noradrenaline and adenylate cyclase responsiveness to β-agonists are decreased[134]. While reversing autonomic remodelling with inhibitors of GRK2 or β-ARs has therapeutic promise, carvedilol, an AR antagonist, can precipitate RVF and careful clinical trials would be required before use in patients[135].

Progressive right ventricular failure

The response of the RV to pulmonary hypertension is the primary determinant of functional capacity and survival[136,137]. Initially the RV undergoes adaptive concentric RVH in response to pressure overload (Fig. 2). Ultimately, maladaptive RVH develops, characterized by reduced RV ejection fraction, dilatation, fibrosis, elevation of end-diastolic pressure and elevated BNP levels. Susceptibility to maladaptive RVH varies among pulmonary hypertension subtypes (greater in scleroderma-associated PAH[138] and less in Eisenmenger syndrome)[139]. Maladaptive RVH is also more common in men. A retrospective Dutch study showed both sexes had similar mPAP reductions after 1 year of pulmonary hypertension-targeted therapy; however, RV ejection fraction improved in women and deteriorated in men[140], a sexual dimorphism that may underlie the male survival disadvantage noted in both the REVEAL and French registries of group 1 pulmonary hypertension[141,142].

RV maladaptation occurs in response to ischaemia[143–145], fibrosis[89,146,147] adrenergic remodelling[133,134], inflammation[107,138,148],

mitochondrial metabolic dysfunction (for example, uncoupled glycolysis or Warburg metabolism[78,84,145,146,149], similar to changes seen in the pulmonary vasculature[63,150,151] increased glutaminolysis[95], and abnormal FAO[94]), and dysregulation of junctophilin 2 and T-tubule structure in RV cardiomyocytes[152] (Fig. 2). RV ischaemia results both from microvascular rarefaction[95,153,154] and impaired right coronary artery perfusion pressure. As pulmonary hypertension worsens and right ventricular pressures approach aortic pressures, right coronary artery perfusion falls. In experimental PAH, placing a supra-aortic band to increase aortic pressure improves coronary perfusion and increases right ventricular function[144]. Lowering right ventricular pressure could also improve ventricular perfusion and function[155]; however, achieving sufficient mPAP reduction is challenging with current therapies.

Diagnosis, screening and prevention

Given the multiple pathways to elevated PAP, its often-insidious nature, and the need for a series of investigations to derive a definitive diagnosis, pulmonary hypertension remains a problematic health issue in individuals of all ages, that is heightened in settings with limited resources. Overall, dyspnoea is the most frequent symptom that drives patients to seek medical attention, and is the most pronounced at diagnosis, usually associated with fatigue, angina, dizziness and oedema[13]. Syncope, particularly during exertion, is also a symptom that occurs in patients with group 1 pulmonary hypertension, particularly in children. The non-specific nature of these symptoms combined with unawareness in patients and health providers leads to delay in diagnosis; even in HIC diagnosis is usually given 2–3 years after the onset of symptoms[10,156–160]. Because delayed diagnosis has serious prognostic implications[7,10], screening of particularly high-risk groups is highly recommended, including patients with systemic sclerosis, portal hypertension, hepatosplenic schistosomiasis, and carriers of mutations in pulmonary hypertension-associated genes[53].

Diagnostic investigations

Routine tests in patients with symptoms and physical findings suggestive of pulmonary hypertension include electrocardiography (ECG), chest radiography, echocardiography and pulmonary function tests[1].

Given the logistical and cost constraints around RHC, echocardiography is the most widely used screening and diagnostic tool in clinical practice worldwide. Transthoracic echocardiography is used to quantify pulmonary hypertension, which is done by deriving a value for eRVSP using the tricuspid regurgitant jet velocity and the modified Bernoulli equation (eRVSP = $4V^2$ (metres per second) + right atrial pressure (millimetres of mercury)) and a qualitative assessment of right atrial pressure (typically 5 or 10 mmHg)[161]. A diagnostic algorithm for evaluation of pulmonary hypertension prior to therapy has been reviewed[48]. Current guidelines recommend confirming other signs of pulmonary hypertension, including assessment of the RV, inferior vena cava and pulmonary flow[1]. As the most prevalent form of pulmonary hypertension worldwide is LHD-PH (group 2), echocardiography is an important method to assess left ventricle parameters (for example, underlying ischaemic CMO or hypertensive heart disease) as potential causative factors in LHD-PH.

Although not possible in all settings (with judicious application advised in paediatric patients), RHC is the gold standard for diagnosis and monitoring of treatment response in pulmonary hypertension. Ideally, every appropriate patient with an echocardiographic diagnosis of pulmonary hypertension should be evaluated by cardiac catheterization if it aids the management decision. RHC also assesses the response to acute vasodilatory testing. This test uses inhaled nitric oxide during RHC in naive patients with iPAH with the goal of identifying patients who may be candidates for long-term calcium[162]. As pulmonary hypertension-targeted therapy is extremely expensive and largely only effective in group 1 and group 4 pulmonary hypertension, correct diagnosis, which includes RHC, is a prerequisite that should be met before initiation of therapy.

High-resolution CT of the lung and CT pulmonary angiography are useful to assess the lung parenchyma (the portion of lungs involved in gas exchange) as well as the pulmonary, bronchial and systemic thoracic vasculature[163]. These are particularly useful to diagnose pulmonary vein stenosis, aortopulmonary window (congenital defect in which there is communication between the aortic artery and the pulmonary artery), and rare conditions such as pulmonary veno-occlusive disease and pulmonary capillary haemangiomatosis[164]. Ventilation–perfusion lung scintigraphy is done to detect abnormal circulation in the pulmonary vessels, and is indicated in all patients with unexplained pulmonary hypertension to assess for the presence of CTEPH[165,166]. Abdominal ultrasonography may be specifically used to rule out portal hypertension or rare congenital extrahepatic portocaval shunt (a cause of reversible pulmonary hypertension).

Post-diagnosis investigation

Six-minute walk distance. Six-minute walk distance (6MWD) is an important measure of exercise capacity in all patients over 6–7 years of age. This practical test closely correlates with the biological parameters of disease severity and clinically relevant exercise tolerance[167]. It is easily replicable in many patients to determine disease progression and the potential effects of treatment.

Biomarkers. Biomarkers have been introduced to complement diagnosis and characterize patients. Low levels of NT-proBNP (usually secreted in response to myocardial wall stress) are strong predictors of survival in both adults and children; children maintaining NT-proBNP levels of <1,200 ng/l during treatment have significantly better survival rates[168].

Diagnosis of paediatric pulmonary hypertension

In most paediatric registries, age at diagnosis varies from 3 to 7 years[31,33,34,36,37], excluding persistent pulmonary hypertension in newborn cases. In most paediatric patients, pulmonary hypertension is NYHA/WHO FC I or II at presentation. Overall, those with LHD-PH have a worse NYHA/WHO FC than those with PAH (pulmonary hypertension is likely to be much more advanced at presentation in children living in a LMIC).

Although children may not always be reliable in reporting symptoms, major symptoms are dyspnoea on exertion and fatigue. Chest pain, near syncope and syncope (in 10–20% of children) are more common in children with iPAH/heritable PAH, while RVF failure with peripheral oedema occurs less frequently than in adults[33] The TOPP registry reported syncope in 25% of children without a shunt; syncope was less frequent in younger children than in older children at diagnosis[30]. Other less common symptoms include chest pain, cyanosis and haemoptysis.

In the presence of a shunt lesion, such as ventricular septal defect or patent ductus arteriosus, PAP can be estimated by measuring the pressure gradient across the defect on echocardiography. Pulmonary vein stenosis is a risk factor for developing severe pulmonary

hypertension in infants with bronchopulmonary dysplasia, and is associated with a significant increase in mortality in these patients[37]. Because RHC requires conscious sedation or general anaesthesia, it is often not performed in infants and small children. The reported risk of adverse events due to catheterization in paediatric pulmonary hypertension ranges from 1.4% to 3.5%, and mortality from 0% to 1.4%[169,170]. The risk increases almost threefold in those under the age of 2 years[31,171]. Thus, cardiac catheterization should be avoided or judiciously used in young children at high risk. When operability for closure of shunts is envisaged, RHC with vasodilator testing is still indicated. However, in resource-limited settings where facilities for performing RHC are not widely available[8,26,172,173], children with shunt lesions may be excluded from surgery by echocardiography[7]. Normal values for the 6MWD have been established for the paediatric population[174]. Shorter 6MWD combined with lower transcutaneous oxygen saturation during the test correlate with higher NYHA/WHO FC, higher NT-proBNP levels and worse transplant-free outcomes in paediatric patients with pulmonary hypertension[167].

Screening

First-degree relatives of all patients with PAH with a genetic mutation known to be implicated in PAH (Box 3) should undergo genetic counselling.

Community-based pulmonary hypertension screening is not standard practice due to the perceived low chance of detection in asymptomatic individuals, and the low capacity to adequately manage those detected. With the need to avoid diagnostic delays and missed diagnoses of treatable precapillary pulmonary hypertension, for patient's survival and quality of life (QoL), portable battery-powered devices must be considered for use outside the hospital environment to assess high-risk populations. However, this requires testing of pragmatic algorithms based on clinical history, ECG, ultrasonography, spirometry and biomarkers, and such devices must be suitable for use by trained non-physicians and community researchers[175]. This approach may prove to be particularly useful in low-resource settings, but the need to proactively detect early forms of pulmonary hypertension applies worldwide. Moreover, the importance of accurate diagnosis prior to therapy is a universal priority, not just restricted to high-income regions.

Prevention

As reflected in its classification, there are multiple pathways to pulmonary hypertension, not all of which are preventable or even fully understood. Indeed, there are minimal data on the population-attributable risk associated with its most common antecedents. However, given that a majority of patients with pulmonary hypertension have LHD-PH (group 2) or LD-PH (group 3), primary prevention is invariably linked to controlling exposure to a series of environmental, metabolic and behavioural risk factors, such as cigarette smoking. Clinically, many patients have components of both group 2 and group 3 disease, probably due to shared risk factors of these groups, and it is impossible to apportion the extent to which lung disease or LHD drives the syndrome[19]. As highlighted by the Global Burden of Disease Study, the relative contribution and importance of each factor will vary according to the socioeconomic status and lifestyle habits in individual populations/regions of the world[176]. From an environmental perspective, reducing exposure to ambient particulate matter pollution, in particular pollution from solid fuels, is a high-priority prevention target on a global basis[177,178]. At the individual level to the population level, risk can be reduced via prevention programmes that markedly reduce blood pressure and LDL cholesterol levels, high-risk dietary behaviours and smoking (including secondhand smoke exposure) rates[176]. Patterns of elevated risk in the predominantly low-income countries of sub-Saharan Africa (where more individuals are affected by a combination of hypertension[179], exposure to indoor air pollution[180] and a range of poverty-related diseases linked to pulmonary hypertension[7,181]) highlight the challenge of developing coherent prevention programmes on a global basis. From a secondary prevention perspective, as with the likely gains from detecting and treating systemic hypertension found in younger individuals[161], there is a cogent argument for applying more proactive surveillance for early forms of pulmonary hypertension — with gold-standard management of contributory LHD[165] and lung disease[166,167] to prevent progressively higher PAP levels and therefore increased mortality[17].

Management

Ideally, management of pulmonary hypertension should be performed in specialized centres hosting multidisciplinary teams that regularly treat patients with severe precapillary pulmonary hypertension (defined by a PVR of >5 WU), who present at high risk of death[1,3]. These centres should include health-care professionals, outpatient clinics, emergency care, an intensive care unit, echocardiography, chest imaging (CT, nuclear medicine), pulmonary function and exercise tests, a cardiac catheterization laboratory, access to genetic counselling and testing, interventional radiology, and cardiothoracic surgery. They should offer easy access to the full range of therapies available in their country and have established care pathways to CTEPH management, lung transplantation and rehabilitation. In addition, they should benefit from expert networking and take advantage of virtual tools such as the clinical patient management system, available in European Reference Networks (ERN-LUNG)[1,3]. Finally, they should be involved in collaborative clinical research, record patient data in registries and undergo regular audits to assess the quality of delivered care. Smooth collaboration with patient associations is an important mission in expert centres[1,3].

General measures and symptomatic treatments

After confirmation of diagnosis, general measures include patient education (including their families), psychosocial support and vaccinations against influenza, pneumococcus and SARS-CoV-2 (refs. 1,3). Symptomatic treatments include low-salt diet, diuretics and long-term oxygen therapy, if required[182]. Therapeutic anticoagulation is proposed on an individual basis, especially in patients with a history of venous thromboembolic pulmonary disease[182]. Patients stabilized on therapy can benefit from supervised cardiopulmonary rehabilitation programmes.

Management of PAH

Group 1 PAH has been the focus of intense drug development implemented in practice guidelines. Less than 10% of patients with iPAH, heritable PAH or drug-associated PAH will benefit from treatment with calcium channel blockers[1,3]. Such responders showed an acute vasodilator response to inhaled nitric oxide, inhaled iloprost or intravenous prostacyclin in initial haemodynamic studies[162]. The majority of patients will be non-responders and should be treated with PAH drugs targeting the prostacyclin, nitric oxide and endothelin pathways. These drugs include oral endothelin receptor antagonists (ERAs); oral phosphodiesterase type 5 inhibitors (PDE5is); oral sGC stimulators; intravenous, subcutaneous or inhaled prostacyclin analogues; and oral prostacyclin receptor agonists[1,3] (Fig. 3). Sotatercept is a biologic agent that traps activin receptor IIA ligands including activins, GDF-8 and

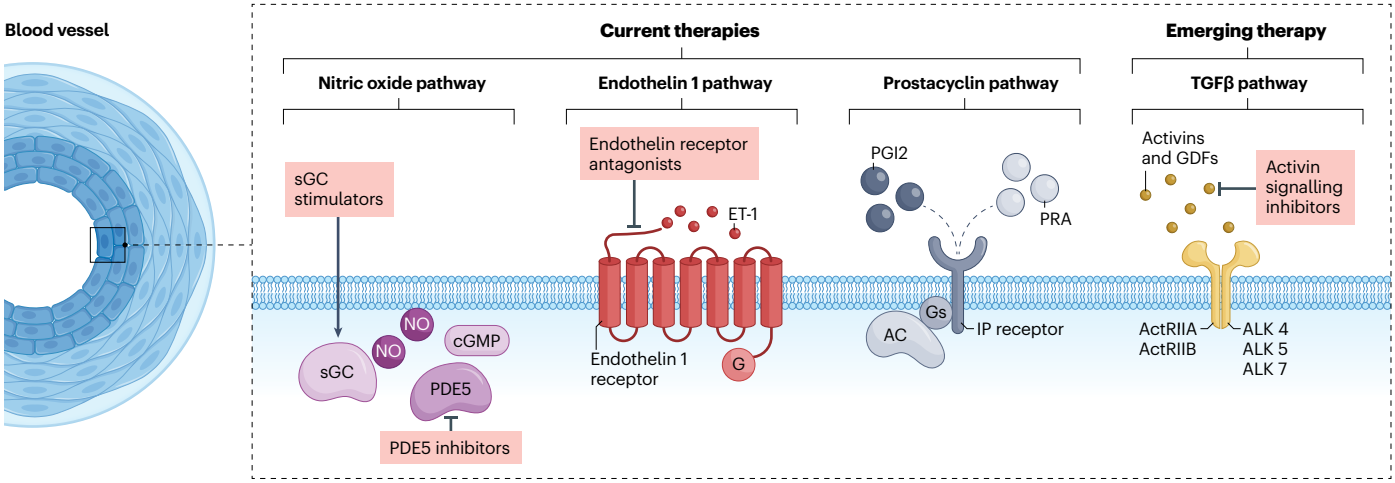


Fig. 3 | Current pulmonary arterial hypertension therapies. The main targets for current therapies in pulmonary arterial hypertension are shown including the prostacyclin, nitric oxide (NO) and endothelin pathways, and an emerging therapy — the activin pathway. The drugs used are represented next to each target. cGMP, cyclic GMP; PDE5, phosphodiesterase type 5; sGC, soluble guanylate cyclase; TGFβ, transforming growth factor-β.

GDF-11; activin type 2 receptors belong to a larger TGFβ receptor family and modulate signals for TGFβ ligands, and are involved in growth, cell differentiation, homeostasis, osteogenesis, apoptosis and many other functions[183]. This activin signalling inhibitor is administered via the subcutaneous route but is not yet approved for the treatment of PAH[58,184].

In newly diagnosed patients without cardiovascular or pulmonary comorbidities, the treatment algorithm is based on a multiparameter risk assessment including FC, 6MWD, biomarkers (BNP or NT-proBNP), echocardiography, cardiac MRI and haemodynamic measures[1,3]. Patients are classified as low risk, intermediate–low risk, intermediate–high risk or high risk of mortality. In patients with severe disease who present at high risk of death, initial triple combination therapy with an ERA, a PDE5i and a parenteral (intravenous or subcutaneous) prostacyclin analogue should be considered, while initial double oral combination therapy including an ERA and a PDE5i is recommended in patients with low or intermediate risk, who represent the majority of patients presenting[185]. All patients with PAH should be re-evaluated 3–6 months after treatment initiation with a simplified four-stratum multiparametric assessment model based on three non-invasive variables (FC, 6MWD and BNP or NT-proBNP), bearing in mind that additional data such as imaging or haemodynamic assessment may be needed to refine the evaluation. In patients at low risk, if it is considered that treatment goals have been met, PAH therapy remains unchanged. In patients on oral dual combination therapy at intermediate–low risk can be offered either the addition of selexipag (a selective non-prostanoid prostacyclin receptor agonist that causes vasodilatation of the pulmonary vasculature) or a switch from a PDE5i to a sGC stimulator (riociguat), which reduces oxidative stress by increasing levels of nitric oxide in the heart and blood vessels. In patients at intermediate–high or high risk of death, escalation to triple therapy should be considered with the addition of a parenteral prostacyclin. Moreover, referral for lung transplantation evaluation should be considered in eligible patients who remain at intermediate–high or high risk on optimized treatment[1,3].

Registries have shown that PAH is often identified in patients over the age of 65 years, many of whom have heart or lung comorbidities[1,3]. A combined left heart PAH phenotype is mostly observed in older women with risk factors for LHD (obesity, diabetes mellitus, hypertension and coronary heart disease)[186]. Most of these patients have echocardiographic signs of left ventricular diastolic dysfunction, while RHC shows precapillary pulmonary hypertension. The effects of PAH medications in such patients have not been well studied. Registry data and subgroup analyses from clinical trials suggest that patients with a left heart phenotype have less clinical improvement than patients with a classic phenotype, while adverse events and treatment discontinuations are more common. The characteristics of patients with pulmonary hypertension have changed over time, with an increasing number of older individuals with PAH who have high rates of comorbidities, such as systemic hypertension (65%), diabetes (22%) and coronary artery disease (25%)[186]. The lung phenotype is mostly observed in older men with a smoking history who present without overt signs of parenchymal lung disease, but a low diffusion capacity for carbon monoxide and hypoxaemia[187]. While these patients are classified as having iPAH by current criteria, they usually respond poorly to PAH therapies. Whether these patients should be considered as having LD-PH is currently debated. In the absence of strong evidence, the current European pulmonary hypertension guidelines recommend a cautious use of PAH medications in older patients with relevant cardiopulmonary comorbidities, starting with oral monotherapy (usually a PDE5i) followed by personalized decision-making[3]. More evidence needs to be generated to fill this important gap.

Pulmonary hypertension associated with left-sided heart disease

In patients with LHD-PH (group 2), the priority is to optimize the management of the cardiac condition. Several PAH medications are detrimental in these patients and, therefore, not recommended[1,3]. In the presence of fluid retention (pulmonary congestion), diuretics are the cornerstone of therapy[188].

Pulmonary hypertension associated with lung diseases

In patients with LD-PH (group 3), optimal management of the underlying respiratory condition is a priority, and should include supplementary

oxygen and non-invasive ventilation, if indicated[189]. There is limited evidence for the use of PAH drugs in these patients. Small studies in pulmonary hypertension associated with COPD or emphysema have provided conflicting results[190]. In the absence of robust evidence, it is recommended that patients with COPD and suspected or confirmed severe pulmonary hypertension should be referred to pulmonary hypertension centres for personalized decision-making[1,3].

More information is available for patients with pulmonary hypertension associated with interstitial lung disease (ILD). Of note, there were concerning safety signals with the use of ambrisentan in patients with idiopathic pulmonary fibrosis and with riociguat in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias[191]. Registry studies suggest that a subset of patients with severe precapillary pulmonary hypertension (defined by a PVR of >5 WU) may benefit from treatment with a PDE5i[192]. A large pulmonary hypertension randomized controlled trial showed improvements in 6MWD with inhaled treprostinil, a vasodilator and platelet aggregation inhibitor[193]. Inhaled treprostinil may, therefore, be considered for the treatment of patients with ILD and pulmonary hypertension[193], but long-term data are still needed. The routine use of other medications approved for use in PAH is not recommended in patients with ILD and non-severe pulmonary hypertension (PVR <5 WU). In patients with severe pulmonary hypertension and/or severe RV dysfunction, or in patients with uncertainty regarding the treatment of pulmonary hypertension, referral to a pulmonary hypertension centre is recommended to enable careful evaluation, facilitate entry into studies, and consider PAH therapies on a personalized basis. Given the significant effect of pulmonary hypertension in such patients, eligible patients should be referred for lung transplantation evaluation[1,3].

Chronic thromboembolic pulmonary hypertension

The treatment of CTEPH has been revolutionized by a better understanding of its pathophysiology; associating an obstruction of proximal, segmental and subsegmental pulmonary arteries of different degrees with remodelling of the microvasculature similar to complex vascular formations originating from remodelled pulmonary arteries (plexiform lesions) found in PAH[58,194,195]. This has facilitated the development of complementary treatment approaches such as surgical pulmonary endarterectomy (PEA), balloon pulmonary angioplasty (BPA) and drugs approved for use in PAH. Long-term anticoagulation is recommended for patients with CTEPH; vitamin K antagonists have been most widely prescribed, but non-vitamin K oral anticoagulants, such as the Factor Xa inhibitors like rivaroxaban, are often used as alternatives. Importantly, vitamin K antagonists are recommended in patients with antiphospholipid syndrome, an autoimmune disorder that causes abnormal blood clots to form[1,3,194].

Surgical PEA is the treatment of choice in patients with accessible PAH lesions. An expert multidisciplinary team including an experienced PEA surgeon is mandatory for evaluating operability and deciding final treatment[196]. The surgery consists of a bilateral endarterectomy of the pulmonary arteries down to segmental and subsegmental levels in phases of deep hypothermic circulatory arrest. Two randomized controlled trials have demonstrated the efficacy of oral riociguat as well as subcutaneous treprostinil in patients with inoperable CTEPH[197] or in those with persistent/recurrent pulmonary hypertension after PEA[198]. Other PAH therapies, including PDE5is and ERAs, have been used off-label, as their efficacy in inoperable CTEPH has not been demonstrated in clinical trials. Combination therapy, including double oral combination therapy with an ERA and a PDE5i, is common practice in patients with severe haemodynamic compromise and persistent hypotension (systolic blood pressure <90 mmHg or mean arterial pressure <30 mmHg) with decreased cardiac index. In patients with inoperable CTEPH or persistent/recurrent pulmonary hypertension after PEA, BPA is the preferred approach. BPA is effective, but it can cause vascular injury due to wire perforation and lung injury leading to haemoptysis (spitting of blood derived from the lungs or bronchial tubes) and hypoxaemia[199]. There is a learning curve that results in a marked reduction in complications over time; therefore, it should be performed in high-volume centres with well-trained interventional radiologists working in multidisciplinary teams. As lower mPAP and PVR translate into reductions in the rate of complications, pretreatment with PAH therapy is the preferred approach before BPA in patients with a PVR of >4 WU[1,3].

Because CTEPH has a very heterogeneous phenotype in terms of anatomy, the degree of pulmonary hypertension and the lack of a standard patient profile, multimodal approaches utilizing medical therapy, BPA and PEA are proposed in some patients with CTEPH. Using medical therapy in patients eligible for PEA but with a high preoperative PVR remains controversial, as it may delay timely surgery. A number of patients with CTEPH may have persistent or recurrent pulmonary hypertension following PEA, which may also benefit from PAH drugs and/or BPA. Some patients present with mixed anatomical lesions with surgically accessible lesions on one lung and inoperable lesions on the other side; in such cases, a strategy sequentially offering PAH medications, BPA and PEA to decrease the surgical risk and improve the final result should be considered[1,3,194].

Management of paediatric pulmonary hypertension

With respect to treatment, children with CHD often have high rates of left ventricle dysfunction at birth, which affects gas exchange and systemic perfusion, in addition to existing pulmonary hypertension. Children who have intact left ventricle function are more likely to respond to pulmonary vasodilators such as inhaled nitric oxide[200]. A systolic-to-diastolic duration ratio greater than 1:4 is inversely correlated with survival in paediatric pulmonary hypertension[201]. Despite the fact that paediatric forms of pulmonary hypertension have some unique causes and management specificities, there are few randomized trials and regulatory authorizations for the use of PAH drugs in children.

Patient and care-giver empowerment

Patient and care-giver empowerment is a priority of patient organizations and of commissioned reference networks such as the ERN-LUNG, supported by the European Commission[1,3]. A call to action developed by the European Pulmonary Hypertension Association focuses on patients' needs that are not adequately met, including access to expert care, psychosocial support, and clinical research and innovation[116,117]. In that setting, the ERN-LUNG has endorsed and disseminated European pulmonary hypertension guidelines, developed by a multidisciplinary panel that included patient representatives[1,3]. In addition, a lay summary of the European guidelines has been produced in different languages to explain the recommendations for people with pulmonary hypertension, or their family or care-givers[195].

Quality of life

As a heterogeneous condition of multicausality, which affects individuals of all ages, generalizing the effect of pulmonary hypertension on QoL and longevity is difficult. Nevertheless, there are important features common to nearly all forms of pulmonary hypertension. Firstly, with

the exception of children diagnosed with congenital forms of pulmonary hypertension[202], most individuals affected by pulmonary hypertension experience a significant delay before a definitive diagnosis is made[203], thereby creating a frequent and problematic 'disconnect' between symptomology and corrective therapy. Secondly, the two most reported symptoms associated with pulmonary hypertension (dyspnoea and fatigue)[15,203–207] are highly non-specific. Thirdly, when left untreated (that is, when first detected), pulmonary hypertension is typically associated with very poor QoL[208]. Finally, as reflected by contemporary studies of the prognostic effect of elevated pulmonary pressures associated with all forms of pulmonary hypertension[22,209], the risk of premature mortality is high across the disease spectrum.

It is thought that many individuals live with and subsequently die with or from pulmonary hypertension without knowing why they are breathless and fatigued. Those fortunate enough to be diagnosed and treated often wait years for this to happen. Accordingly, in a cohort of 187 individuals (mean age 36.4 years, women to men ratio of 1.7:1, and 75% NYHA FC III–IV) being managed for pulmonary hypertension in expert centres in the USA in the 1980s, one in ten reported symptoms of up to 20 years duration[206]. Overall, the time from reported symptom onset to diagnosis was close to 24 months. Equivalent data from newer studies, including a French registry report[205] and the REVEAL Registry in North America[204], suggest that pulmonary hypertension (particularly iPAH) remains difficult to detect (and treat) proactively, given that the time from symptom onset to diagnosis ranged from 2.3 to 2.8 years.

The most common non-specific instruments used to assess the QoL of adults with PAH (noting that few studies consider all forms of pulmonary hypertension together) are the generic Short Form 36 Health Survey (SF-36) tool and the heart failure-specific Minnesota Living with Heart Failure Questionnaire (MLHFQ)[210]. Instruments specifically developed for and validated in patients with pulmonary hypertension include the Cambridge Pulmonary Hypertension Outcome Review (CAMPHOR), Pulmonary Arterial Hypertension–Symptoms and Impact (PAH-SYMPACT) and EmPHasis-10 (ref. 210). To assess dyspnoea as a measure of QoL, exercise tolerance is both subjectively reported using the NYHA/WHO FC I–IV scoring system[211], as well as objectively measured using the 6MWD test[212].

For assessing the QoL of paediatric patients and their parents, the Pediatric Quality of Life (PedsQL) tool is commonly used[213]. One study reported on four QoL domains (physical, emotional, social and school functioning) among paediatric patients with different pulmonary hypertension subtypes aged 2–18 years and their parents using the PedsQL tool[213]. The cohort had significantly lower QoL scores compared with health norms in healthy children, and lower scores compared with equivalent children/parents with CHD or malignancy.

Box 4

Research, care and advocacy priorities

Increase availability of data

- Establish collaborative networks to define a true global registry of pulmonary hypertension
- Invest in deep phenotyping (including molecular rather than clinical phenotyping) to define and select patients for interventional studies
- Establish novel new biomarkers for both entry into enrichment studies and outcome measures
- Establish novel new clinical trial designs, including pragmatic clinical trials

Improve access and care

- Prioritize resource allocation in low-income and middle-income countries (LMICs) to improve the ability to perform diagnosis including right heart catheterization and different imaging modalities, as well as to perform molecular and genetic/epigenetic analysis for research in standard care
- Partner with industry and regulatory bodies to speed up the development of novel new and repurposed drugs to treat pulmonary hypertension effectively
- Define a personalized approach to treating patients based on their molecular phenotype
- Encourage comprehensive research projects (with basic, translational and clinical scientists) to improve understanding of the underlying mechanisms of disease progression
- Promote early detection from presenting symptoms so treatment commences earlier
- Improve the ability and cost of diagnosing pulmonary hypertension at the population level, particularly in low-income countries
- Promote prevention and discovery of effective novel therapies for patients with pulmonary hypertension associated with left-sided heart disease and respiratory disease

Advocate for equity in research and care

- Improve early recognition/diagnosis and access to drug therapy globally, particularly in low-income countries
- Encourage the Global Burden of Disease Study and WHO to recognize pulmonary hypertension as a significant disease burden globally
- Work with patient-based organizations to best represent and address the spectrum of problems of patients and carers
- Promote repurposing and discovery of drugs for neglected infectious and non-communicable diseases that lead to pulmonary hypertension
- Engage with industry (primarily pharmaceutical companies but also other cardiorespiratory companies) to encourage them to become more committed to providing diagnostics, drugs and devices to LMICs for research and care
- Increase the focus of clinical and basic researchers and pharmaceutical companies to improve our understanding of the mechanisms in pulmonary hypertension associated with diseases such as schistosomiasis and TB-associated pulmonary hypertension, beyond the scope of such strategies for high-income countries

A systematic search using the Cochrane guidelines for conducting a meta-analysis revealed 11 studies evaluating the QoL of patients with PAH at baseline and at 12 weeks after an intervention using the SF-36, MLHFQ and CAMPHOR. The groups mean physical component score (SF-36) was 37.2 (95% CI 33.24–41.16) and the heterogeneity coefficient (I^2) was 97.71% ($P < 0.001$). Regarding the mental component, the mean score (SF-36) was 46.38 (95% CI 44.21–48.56) and the heterogeneity coefficient was 87.92% ($P < 0.001$). These results indicate improved QoL 12 weeks after the intervention; the greatest improvement in QoL was observed in patients treated with bosentan and iloprost, and the smallest improvement was observed in patients treated with epoprostenol[208].

Across all its subtypes, mortality rates associated with pulmonary hypertension remain stubbornly high[23,196]. Younger individuals (typically more women than men)[203] clearly have the most to lose in terms of LYL. However, in a recent clinical cohort study in 70,826 men (aged 61.3 ± 17.7 years) and 84,130 women (aged 61.3 ± 17.7 years), compared with individuals with no evidence of pulmonary hypertension, the risks of all-cause and cardiovascular-related mortality were 1.90-fold (95% CI 1.84–1.96) and 1.85-fold (95% CI 1.74–1.97) higher, respectively, in those with an eRVSP in the range 35.0–39.9 mmHg (that is, indicative of mild pulmonary hypertension)[26,202]. While premature mortality rose with pulmonary hypertension severity (from 46.7% to 79.2%), men and women with an eRVSP in the range 30.0–39.9 mmHg accounted for 58% and 53% of all LYL within the cohort[26].

In summary, patients with PAH tend to have a poor QoL, mostly due to physical activity limitations, which can be improved by therapeutic interventions, particularly pharmaceutical agents. In addition, patients with PAH tend to suffer from depression, anxiety, stress and sleep disorders[208].

Outlook

The improvements in definition and classification, increased access to non-invasive screening and early diagnosis tools, refinement of diagnostic guidelines, and discovery of new therapeutic targets and new and adjuvant drugs are important milestones towards improving care and outcomes in patients with pulmonary hypertension, in whatever region of the world they live. While there are reasons to celebrate progress in understanding the mechanisms and the arrival of new treatments for PAH and CTEPH, there are still major gaps in basic, clinical and translational knowledge about pulmonary hypertension that affects a large proportion of the world's population. These include uncovering the pathways to pulmonary hypertension due to chronic exposure to environmental hazards (indoor air pollution in many vulnerable households being a concern) and endemic infectious agents (HIV, tuberculosis, COVID-19 and schistosomiasis)[214,215]. Addressing these major geographic and social inequities in pulmonary hypertension research is important to account for the expected variations in natural history and outcomes in individuals with different genetic backgrounds, nutritional status and exposure to multimorbidity.

Population-based registries are the best tool to uncover the burden of pulmonary hypertension, but there are several challenges that hamper the implementation of such a strategy worldwide. In this context, hospital-based registries have been the most important source of information for health policy and planning, despite only providing an indication of demand. We suggest that task-shifting and pragmatic screening algorithms — mirroring what has been done for community-based screening for neglected cardiovascular diseases such as RHD[169] and endomyocardial fibrosis[216] — should be developed.

The multi-country hospital-based registry in Africa revealed a unique pattern of environmental risks, low access to health care and ill-equipped health systems, which contribute to delay in pulmonary hypertension diagnosis and management. Importantly, it confirmed a high occurrence of pulmonary vascular disease that could be prevented with improvements in community awareness, health literacy and health system strengthening. Efforts to improve early detection may benefit from the reframing of pulmonary hypertension classification, the acceptance of pragmatic screening and diagnostic algorithms[173,175], and selection of interventions that can be delivered by non-specialists to manage increased levels of PAP detected by determining eRVSP.

Research priorities should include the perspectives of patients, carers and clinicians[217] (Box 4). Clinical research based on collection of longitudinal data with deep phenotyping should be promoted — including clinical work-up, imaging, and haemodynamic, physiological and molecular characterization — to enable dataset integration and new analytical approaches, and the design of master clinical trials[176].

The use of a multisectoral approach should result in implementation of public health measures to address pulmonary vascular diseases. These include reinforcement of routine vaccination, control of endemic infections (TB, schistosomiasis, HIV), smoking cessation campaigns and mass drug administration against parasitic diseases; increasing access to affordable clean energy; health provider education on the long-term sequelae of endemic diseases that may lead to pulmonary hypertension; and early detection and timely management of those diagnosed. Because longer diagnostic intervals seem to be related to higher mortality rates, focus on addressing inequities in diagnosis and management is essential to reduce the inequities in the pulmonary hypertension burden. This entails identifying new therapeutic targets for neglected conditions, promoting drug discovery and repurposing available drugs.

Pulmonary hypertension is not a rare disease, but its rarest form (PAH) has attracted the greatest attention and development of effective therapeutic agents[13]. Advances in pulmonary hypertension prevention and care require the research and clinical communities to not only focus on PAH and CTEPH, but also to address the burden of pulmonary vascular disease that complicates many common conditions, especially LHD and lung disease, as well as several neglected tropical diseases. Balancing the response to the full spectrum, distribution and burden of pulmonary hypertension requires greater engagement of health-care providers, policymakers and professional associations, and commitment from commercial/industry groups to develop novel, evidence-based therapies that cost-effectively treat more prevalent forms of pulmonary hypertension (including LHD-PH and LD-PH). Regional and global networks such as the World Symposia on Pulmonary Hypertension Association, the Pulmonary Vascular Research Institute, cardiac/pulmonary professional societies (the European Respiratory Society, the European Society of Cardiology, the Global Alliance against Respiratory Diseases, the Pan-African Society of Cardiology, the Cardiac Surgery Intersociety Alliance and the World Heart Federation), the Non-Communicable Diseases and Injury of Poverty Network, patient associations and the WHO are crucial to advocate for bridging the current gaps in care and building on the existing opportunities to reduce the burden of pulmonary hypertension worldwide.

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