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REVIEW

Pulmonary hypertension: the science behind the disease spectrum

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ABSTRACT: Pulmonary hypertension (PH) is a complex, multifactorial disorder divided into five major subtypes according to pathological, pathophysiological and therapeutic characteristics. Although there are distinct differences between the PH categories, a number of processes are common to the pathology of all subtypes.

Vasoconstriction, as a result of endothelial dysfunction and an imbalance in the levels of vasoactive mediators, is a well-characterised contributory mechanism. Excessive cell proliferation and impaired apoptosis in pulmonary vessels leading to structural remodelling is most evident in pulmonary arterial hypertension (PAH), and several factors have been implicated, including mitochondrial dysfunction and mutations in bone morphogenetic protein receptor type 2. Inflammation plays a key role in the development of PH, with increased levels of many cytokines and chemokines in affected patients. Exciting insights into the role of angiogenesis and bone marrow-derived endothelial progenitor cells in disease progression have also recently been revealed. Furthermore, there is increasing interest in changes in the right ventricle in PH and the role of metabolic abnormalities.

Despite considerable progress in our understanding of the molecular mechanisms of PH, further research is required to unravel and integrate the molecular changes into a better understanding of the pathophysiology of PH, particularly in non-PAH, to put us in a better position to use this knowledge for improved treatments.

KEYWORDS: Angiogenesis, endothelial dysfunction, inflammation, pulmonary arteries, vascular remodelling, vasoconstriction

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Pulmonary hypertension (PH) is defined by an elevated resting mean pulmonary artery pressure >25 mmHg. It is a complex, multifactorial disorder that leads to overload of the right ventricle and progressive right heart dysfunction [1–3].

The Dana Point classification divides PH into five major subtypes according to pathological, pathophysiological and therapeutic characteristics: 1) pulmonary arterial hypertension (PAH); 2) PH due to left heart disease; 3) PH due to interstitial lung diseases and/or hypoxia (PH-ILD); 4) chronic thromboembolic PH (CTEPH); and 5) PH with unclear and/or multifactorial mechanisms [1]. PAH represents only ~10% of the PH population, but has attracted the most interest with respect to understanding the underlying pathophysiology of PH and the development of new treatments [2].

Exciting developments in recent years include insights into the genetic basis of heritable PAH due to mutations in members of the transforming growth factor-β pathway (*e.g.* bone morphogenetic protein receptor type 2 (BMPR2)) [4, 5]. Further discoveries have highlighted the major roles played by excessive vascular cell growth and inflammation, and recruitment and infiltration of circulating cells in PH. Moreover, new knowledge has been gained into the well-established roles of vasoconstriction and thrombosis in disease pathogenesis [6].

This review will provide a broad overview of some of the underlying mechanisms that lead to PH, focusing on the various changes in signalling pathways that drive disease progression.

DISEASE OVERVIEW

Although the factors responsible for disease initiation differ somewhat between the subcategories of PH, vasoconstriction, endothelial dysfunction, dysregulated cell growth, inflammation and thrombosis all participate to a greater or lesser extent in driving disease progression

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(fig. 1). The pathological changes witnessed in the individual subtypes of PH are summarised in table 1, together with contributory disease mechanisms.

VASOCONSTRICTION

The lung is both a source of, and target for, a number of vasoactive factors. One of the characteristics of PH is an imbalance in tissue and circulating levels of these vasoactive mediators as a result of endothelial dysfunction.

Prostaglandin I_2

Prostaglandin (PG)H_2, generated from arachidonic acid by fatty acid cyclooxygenase, is a substrate for both PGI_2 synthase and thromboxane synthase. PGI_2 synthase is expressed in pulmonary vascular endothelium and generates prostacyclin PGI_2, which acts to relax smooth muscle cells (SMCs) and inhibit platelet aggregation *via* the stimulation of cAMP production [7]. Thromboxane synthase generates thromboxane A_2, which stimulates vasoconstriction and platelet aggregation *via* thromboxane/PG receptors. In PAH, levels of prostacyclin are reduced and thromboxane levels are increased [8]. An early success in the treatment of PAH was the introduction of prostacyclin replacement therapy.

Nitric oxide

Nitric oxide (NO) is synthesised in the endothelium from L-arginine by endothelial NO synthase (eNOS) [9]. In pulmonary artery SMCs, NO stimulates soluble guanylate cyclase (sGC) to produce cyclic GMP (cGMP), which has vasodilatory and antiproliferative properties. The eNOS/NO/sGC/cGMP axis is the principal mediator of endothelium-dependent vasodilation in the pulmonary circulation [9]. Consequently, the role of this pathway in PH is subject to intense interest, with a view to exploiting it therapeutically.

All forms of PH are believed to be a state of reduced NO bioavailability, as a result of reduced NO synthase (NOS) expression [10], oxidative stress [11] and inhibition of NO synthesis [12]. Oxidative stress increases the production of free radicals, such as superoxide, which readily react with NO to form peroxynitrite, reducing NO levels. Asymmetric dimethylarginine (ADMA) is an endogenous competitive inhibitor of NOS. Elevated levels have been found in patients with idiopathic PAH (IPAH), CTEPH, PAH related to sickle cell disease and PAH related to systemic sclerosis (SSc) [12, 13]. Moreover, there is a correlation between ADMA levels and survival in CTEPH patients. ADMA has been implicated in the control of a range of pulmonary cell functions *via* direct effects on gene expression and protein function, or *via* inhibition of NOS and secondary NO generation [12]. Lung tissues from patients with IPAH also show impaired expression of dimethylarginine dimethylaminohydrolase (specifically DDAH2), the enzyme responsible for the hydrolysis and degradation of ADMA [12]. Restoring expression of DDAH2 in PAH may be an avenue that can be exploited medically [14].

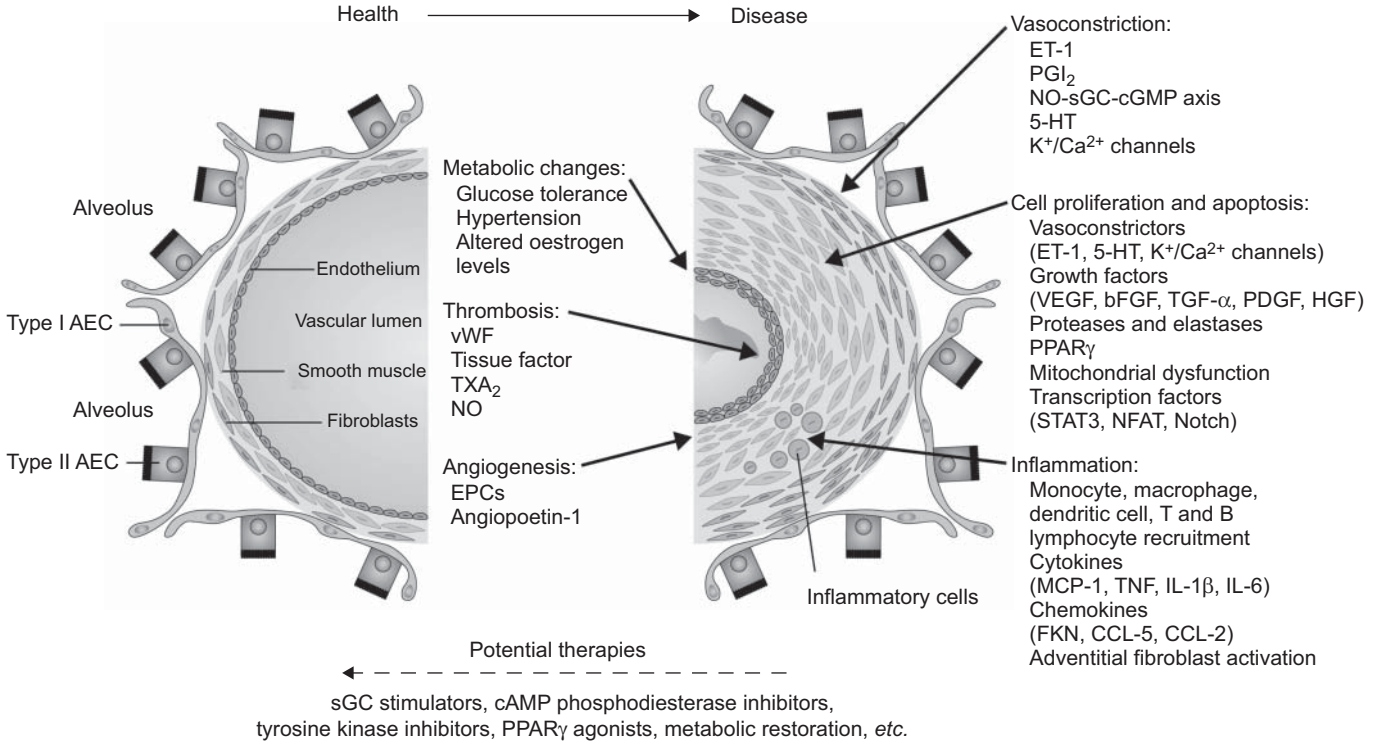

FIGURE 1. The key pathological mechanisms underlying vascular changes in pulmonary hypertension (PH). Potential new therapies for PH are also indicated. AEC: alveolar epithelial cell; vWF: von Willebrand factor; TXA_2: thromboxane A_2; NO: nitric oxide; EPC: endothelial progenitor cell; ET-1: endothelin-1; PGI_2: prostaglandin I_2; sGC: soluble guanylate cyclase; cGMP: cyclic guanosine monophosphate; 5-HT: 5-hydroxytryptamine; VEGF: vascular endothelial growth factor; bFGF: basic fibroblast growth factor; TGF-α: transforming growth factor-α; PDGF: platelet-derived growth factor; HGF: hepatocyte growth factor; PPARγ: peroxisome proliferator-activated receptor-γ; STAT3: signal transducer and activator of transcription 3; NFAT: nuclear factor of activated T-cells; MCP-1: monocyte chemoattractant protein-1; TNF: tumour necrosis factor; IL: interleukin; FKN: fractalkine; CCL: chemokine ligand; cAMP: cyclic adenosine monophosphate. Reproduced from [6] with permission from the publisher.

TABLE 1 Pathological changes and disease mechanisms in pulmonary hypertension (PH) subtypes

PH subtype	Pathological changes	Contributory mechanisms
PAH	Pathological lesions in distal pulmonary arteries	Endothelial dysfunction, leading to changes in vasoactive and growth regulatory factors
	Medial hypertrophy	Vascular cell proliferation
	Intimal proliferative and fibrotic changes	Inflammation
	Adventitial thickening with perivascular inflammatory infiltrates and thrombotic lesions	Thrombosis
PH-LHD	Enlarged and thickened pulmonary veins	Vasoconstrictive reflexes arising from stretch receptors localised in the left atrium and pulmonary veins
	Pulmonary capillary dilatation	Endothelial dysfunction
	Interstitial oedema	Vasoconstriction
	Alveolar haemorrhage	Proliferative remodelling of the pulmonary vessel wall
	Lymphatic vessel and lymph node enlargement	
	Medial hypertrophy and intimal fibrosis of distal pulmonary arteries	
PH-ILD	Medial hypertrophy	Hypoxic vasoconstriction
	Intimal obstructive proliferation of the distal pulmonary arteries	Endothelial dysfunction leading to imbalance in vasoactive signalling molecules
	Destruction of vascular bed in areas subject to emphysema or fibrosis	Mechanical stress of hyperinflated lungs
		Capillary loss
		Inflammation
		Toxic effects of cigarette smoke
CTEPH	Persistent organised thrombi in the medial layer of the pulmonary vasculature	Non-resolution of emboli
	Vessel occlusion	Endothelial dysfunction from shear stress, pressure and inflammation
	Remodelling of the major pulmonary vasculature	Cytokine release
	Small-vessel pulmonary arteriopathy (indistinguishable from changes seen in PAH)	*In situ* thrombosis
		Vasculotrophic mediator release

PAH: pulmonary arterial hypertension; LHD: left heart disease; ILD: interstitial lung disease; CTEPH: chronic thromboembolic PH. Modified from [1].

Reduced NO bioavailability lowers tissue cGMP levels. Increased expression of the cGMP-degrading enzyme phosphodiesterase type 5 (PDE5), both in SMCs and the right ventricle, compounds this [15]. PDE5 inhibition has proven to be an effective therapeutic strategy for some, but not all, forms of PAH [9].

Other factors that signal through cGMP have attracted interest for their contribution to the pathophysiology of PH. The natriuretic peptides (atrial, brain and C-type natriuretic peptides; ANP, BNP and CNP, respectively) have been studied thoroughly. Circulating plasma levels of ANP and BNP reflect cardiac workload and BNP levels are used clinically to monitor patients.

Recently, the receptor APJ and its ligand apelin, of which NO is a downstream target, have been implicated in PH [16]. Apelin is a potent regulator of cardiovascular function and is highly expressed in the pulmonary vasculature [16]. Serum levels of apelin are reduced in patients with PH *versus* controls and apelin-null mice develop more severe hypoxia-induced PH than wild-type mice due to reduced serum nitrate levels and downregulation of eNOS [16].

Endothelin-1

Endothelin (ET)-1 regulates vascular tone by signalling *via* ET_A and ET_B receptors located on pulmonary artery SMCs, acting as a vasoconstrictor and inducing cell proliferation [17]. ET-1 levels are increased in the lungs and circulation of patients with PAH and CTEPH, as well as PH associated with chronic obstructive pulmonary disease (COPD), ILD, SSc, pulmonary sarcoidosis and congestive heart failure [18–20]. In addition to acting as a vasoconstrictor, ET-1 can also induce fibrogenesis *via* interaction with matrix metalloproteinase (MMP) [21, 22]. The ET_B receptor on endothelial cells is involved in the release of NO and prostacyclin [23]. This has raised debate about the relative value of selective inhibition of ET_A over inhibition of both ET receptor subtypes in PH [17]. The coincidental change in ET receptor subtype expression with the onset of disease complicates that debate [19]. At present there is no clinical evidence favouring selective pharmacological inhibition.

5-Hydroxytryptamine

5-Hydroxytryptamine (5-HT) is a potent vasoconstrictor whose production is increased in patients with PAH [24]. Serotonin, synthesised in the endothelial cells of the pulmonary artery, can act on underlying pulmonary arterial SMCs and pulmonary arterial fibroblasts in a paracrine fashion, causing constriction and remodelling. These effects of serotonin can be mediated through both the serotonin transporter and serotonin receptors. Abnormalities in endothelial cell-SMC cross-talk have been linked to enhanced endothelial production of 5-HT, transport and paracrine activity in adjacent pulmonary vascular SMCs in patients with IPAH [25, 26]. While studies

in animal models have supported an important role for 5-HT in PH, its value as a drug target in humans remains unclear.

K^+ channels/Ca^{2+} channels

In PAH, altered function of K^+ channels and Ca^{2+} channels has been linked to changes in pulmonary vascular tone, dysregulation of cellular homeostasis and promotion of proliferation in SMCs [27, 28]. The expression and activity of voltage-gated K^+ channels (most notably Kv1.5) is reduced in PAH, which can lead to induction of muscle contraction *via* Ca^{2+}-calmodulin and myosin light chain kinase, and vascular remodelling by altering the balance between apoptosis and proliferation. Ca^{2+} signalling through transient receptor potential (TRP) ion channels is thought to have an important role in IPAH, where TRPC3 and TRPC6 expression are upregulated in pulmonary arterial SMCs.

CELL PROLIFERATION AND APOPTOSIS

Structural remodelling of pulmonary vessels is particularly evident in PAH and is characterised by excessive cell proliferation and impaired apoptosis. Vascular remodelling is also seen in CTEPH, sharing many of the cellular features of PAH, and to a lesser extent in PH associated with hypoxia.

Several signalling pathways have been implicated in the development of a pro-proliferation/anti-apoptotic cell phenotype. The term ''mitochondrial remodelling'' is used to describe the metabolic changes that occur in proliferating/apoptosis-resistant vascular endothelial cells in PAH, whereby ATP synthesis is generated by glycolysis rather than oxidative phosphorylation [29, 30]. Endothelial cells and SMCs from patients with PAH exhibit dysmorphic and hyperpolarised mitochondria and a glycolytic shift in metabolism [30]. Reversal of this metabolic remodelling may offer a treatment for PAH [30, 31].

Mutations in BMPR2, ALK-1 and endoglin predispose to PAH and suggest novel pathways for treating the disease [4, 32]. However, it is clear that these mutations alone do not cause PAH and other factors are required to initiate the disease.

Vasoconstrictors

Some vasoconstrictor factors, including ET-1 and 5-HT, influence vascular proliferation and, as a consequence, are hypothesised to have a role in vascular remodelling in PH [26, 33]. The expression and function of membrane K^+ channels also plays an important role in regulating pulmonary artery SMC proliferation and apoptosis. Cytosolic K^+ can inhibit endogenous caspases and nucleases and suppress mitochondrial cytochrome c release. K^+ channel inhibition inhibits apoptosis, but also leads to membrane depolarisation and an influx of Ca^{2+}, an obligatory messenger for cell-cycle progression and proliferation [34].

Growth factors

A number of growth factors act as potent mitogens and chemoattractants for vascular cells, such as SMCs, fibroblasts and endothelial cells [2, 3]. Activation of extracellular tyrosine kinase receptors by growth factors initiates major intracellular signalling cascades, resulting in cellular proliferation, migration and resistance to apoptosis [2, 3].

Increased vascular endothelial growth factor (VEGF) and VEGF receptor 2 are expressed in the plexiform lesions of patients with PAH and pulmonary arteries of patients with COPD [35–37]. Increased plasma and urine basic fibroblast growth factor (FGF) levels have been recorded in patients with PAH [38]. Endothelial cell-derived FGF2 contributes to the progression of pulmonary vascular disease in humans and rodents [39]. Several other growth factors, including transforming growth factor-α, platelet-derived growth factor (PDGF) and hepatocyte growth factor, have been implicated in PH, although further investigation is needed to understand their involvement in PH in humans [2]. Studies with tyrosine kinase inhibitors in patients with PAH are underway and will shed light on this area.

Proteases and elastases

MMPs have key roles in modulating structural extracellular matrix proteins and are upregulated in remodelled lung vasculature of patients with IPAH, PAH and PH of unexplained causes [38, 40]. Endogenous elastases can release mitogens and growth factors which may also contribute to the development of PAH [41]. Increased elastolytic activity may be an early feature of PH.

Notch

Notch signalling is involved in several stages of vascular development, including vasculogenesis, angiogenesis and differentiation of vascular SMCs [42, 43]. In SMCs, Notch-3 regulates SMC maturation, promotes proliferation of vascular SMCs and inhibits the expression of contractile protein genes [42, 43]. Human PH is characterised by overexpression of Notch-3 in small pulmonary artery SMCs and the severity of disease in humans and rodents correlates with the amount of Notch-3 protein in the lung [44].

Peroxisome proliferator-activated receptor-γ

Peroxisome proliferator-activated receptor (PPAR)γ has a crucial role in cell growth, inflammation and angiogenesis in many tissues, including vascular endothelial cells, vascular SMCs and macrophages [45]. In the angiogenic plexiform lesions in lungs from patients with PAH, expression is reduced compared with pulmonary vascular endothelial cells from healthy lungs [46]. In mice, conditional knockout of PPARγ in SMCs or endothelial cells resulted in the spontaneous development of PH [47]. PPARγ is also important for BMP2-mediated inhibition of PDGF-induced vascular SMC proliferation and reduces levels of ET-1 and ADMA [48]. Thus, PPARγ agonists are under evaluation as a novel approach to treating PAH.

Apoptosis

It is hypothesised that the formation of plexiform lesions in PAH is a result of widespread endothelial apoptosis during the early stages of the disease, resulting in the selection and proliferation of apoptosis-resistant endothelial precursor cells [2, 3]. Many factors potentially drive this proliferation, including changes in BMPR2, mitochondrial abnormalities, expression of anti-apoptotic and pro-survival proteins, expression/activity of serotonin transporter and PDGF receptors, tyrosine kinase activation and K^+ channels [2, 3]. The sustainability of an excess proliferation/impaired apoptosis phenotype also requires the activation of pro-survival transcription

factors such as STAT3 (signal transducer and activator of transcription 3) and NFAT (nuclear factor of activated T-cells), both of which have been linked to PAH [2].

INFLAMMATION

Inflammation has been shown to contribute to the progression of PH, and has been implicated as a triggering factor in PAH [49]. Monocytes, macrophages, T and B lymphocytes and dendritic cells are found in plexiform lesions and other vascular lesions of PAH-affected human lungs, together with autoantibodies to endothelial cells and fibroblasts.

Levels of cytokines and chemokines are raised in the blood of patients with PAH, and in some cases, correlate with the magnitude of PH [50, 51]. Increased circulating levels of monocyte chemoattractant protein 1, tumour necrosis factor, interleukin (IL)-1β and IL-6 are found in patients with IPAH. Chemokines shown to be increased in PAH include fractalkine, chemokine ligand (CCL)-5 and CCL-2. Chemokines have a major role in the various steps of leukocyte recruitment, including the initial reversible adherence to the endothelium, subsequent activation, firm adherence and extravasation into the inflamed tissue [52].

In PH, recent data suggest that perivascular inflammation may be sustained through the activation of adventitial fibroblasts, which induce accumulation, retention and activation of monocytes and macrophages. Current thinking is that epigenetic changes in these cells sustain the production of proinflammatory cytokines and chemokines [53].

THROMBOSIS

CTEPH is not simply a consequence of vascular obstruction from thromboemboli. Recent registry data suggest that ~25% of patients have no history of acute pulmonary embolus [54]. A working hypothesis views CTEPH as a primary pulmonary vascular arteriopathy with endothelial dysfunction, triggered by overt or occult pulmonary embolism, leading to secondary *in situ* thrombosis. Changes in distal microvasculature similar to that seen in IPAH contribute to the elevated pulmonary vascular resistance [55], and the extent of distal vessel remodelling determines the potential for recovery after thromboendarterectomy [56]. It is recognised that *in situ* thrombosis is a common finding in severe PH from other causes. Distinguishing patients with CTEPH from IPAH can be problematic.

Risk factors for CTEPH are covered in detail in the review by KIM and LANG [57] in this issue of the *European Respiratory Review*, and include previous pulmonary embolism, ventriculo-atrial shunts, splenectomy and chronic inflammatory disorders [58]. Genetic factors may be important in some patients but deficiencies in traditional pro-thrombotic factors such as anti-thrombin, protein S or protein C, or alterations in fibrinolytic pathways do not appear to have a role in CTEPH pathogenesis [59, 60]. Anti-phospholipid antibodies are more prevalent in CTEPH than PAH [60]. Plasma factor VIII levels may also be higher [61].

Endothelial dysfunction predisposes to intravascular coagulation in some types of PH [62]. Thrombosis is a common feature of PAH [63], where the activity of von Willebrand factor is increased [64]. Patients with IPAH have been shown to possess a hypercoagulable phenotype and tissue factor is strongly expressed in the pulmonary vasculature of such patients [65]. Platelet aggregation might also be increased as a result of imbalance in vasoactive mediators secondary to endothelial dysfunction: thromboxane A2 is pro-aggregatory, while NO and prostacyclin inhibit aggregation [6].

ANGIOGENIC FACTORS

The appearance of the plexiform lesion, suggestive of disordered angiogenesis, has raised the possibility of a role for pro-angiogenic factors in the pathogenesis of PAH [37]. However, the precise role of angiogenesis in the progression of PH remains to be elucidated.

Bone marrow-derived endothelial progenitor cells maintain endothelial integrity and function, repair endothelial injury and participate directly in vasculogenesis and angiogenesis in systemic vascular beds [66]. Patients with IPAH show altered levels of circulating pro-angiogenic progenitor cells compared with healthy individuals. At present there is no consistent view as to whether levels are reduced [67] or elevated [68] in IPAH, but levels are reduced in PH associated with congenital heart disease [69]. Angiopoetin-1, a signalling molecule involved in angiogenesis and SMC proliferation and experimentally linked to PH, has been reported to be strongly upregulated in the lungs of patients with various forms of PH, correlating directly with the severity of disease [69]. Further research is required to establish the precise role of this molecule in PH.

INSULIN RESISTANCE, OBESITY AND SEX HORMONES

Many patients with PH due to pulmonary venous hypertension display clinical features of the metabolic syndrome: obesity, hypertension, diabetes mellitus and hypercholesterolaemia [70]. Systemic hypertension leading to left ventricular end-diastolic hypertension raises pulmonary vascular pressure and may result in reactive vasoconstriction. Pulmonary venous hypertension is often misdiagnosed in such patients as PAH, which is an important distinction for clinical decision making. Glucose intolerance is often missed in PAH [71]. These data, alongside studies showing PH development in PPARγ-deficient mice and adiponectin-deficient mice, point to the need for a better understanding of the role of insulin resistance in the development of PH. A link with obesity, with or without insulin resistance, also needs further study.

Both idiopathic and familial PAH are more common in females, whereas animal studies suggest a protective effect from oestrogen in PH [72]. Recent data suggest that the vascular protective effects of 17b-estradiol (oestradiol; E2) are mediated largely by its downstream metabolites [72]. Oestradiol is metabolised to 2-hydroxyestradiol (2HE) by CYP1A1/CYP1B1, and 2HE is converted to 2-methoxyestradiol (2ME) by catechol-O-methyl transferase. 2ME has anti-mitogenic, anti-angiogenic and pro-apoptotic properties in vascular endothelial cells, SMCs and fibroblasts (in contrast to E2, which is pro-mitogenic, pro-angiogenic and anti-apoptotic). Interestingly, decreased expression of the oestrogen-metabolising enzyme CYP1B1, leading to altered oestrogen metabolism, has also been reported in female PAH patients harbouring a *BMPRII* mutation compared with unaffected female carriers [73].

THE RIGHT VENTRICLE IN PH

Right ventricular hypertrophy (RVH) develops in PH as a result of the right ventricle working against increased resistance in the pulmonary circulation [74]. Initially, RVH is a compensatory mechanism but persistent pressure overload is associated with re-expression of fetal-type contractile proteins and changes in Ca^{2+} handling and energy generation, resulting in decreased cardiomyocyte contractility. The development of right heart failure is accelerated by maladaptive neurohormonal signalling, the generation of reactive oxygen and nitrogen species, ischaemia and exaggerated inflammatory responses, and associated cardiac fibrosis [74].

Right ventricular function is a major determinant of prognosis in PH. The factors that determine whether the right ventricle adapts or dilates to the pressure overload are poorly understood, but genetic factors are likely to play a role. Elevated plasma levels of circulating BNP, secreted by the hypertrophied myocardium, correlate with prognosis in cohort studies but perform less well as at the individual patient level as a guide to day-to-day management.

It is clear from studies in lung transplant patients that right ventricle function can improve with effective reduction in pressure load. It has been suggested that the myocardium in PH may be hibernating, with a metabolic shift from oxidative mitochondrial metabolism to the less energy-efficient glycolytic metabolism, perhaps related to cardiac ischaemia [75, 76]. If so, strategies that reduce ischaemia and/or restore normal oxidative phosphorylation (as opposed to glycolytic metabolism) are a therapeutic option for improving function and prognosis.

CONCLUSIONS

Multiple factors are involved in the pathophysiology of PH. Disease progression is driven by a combination of changes in the balance of vasoactive mediators, altered cell proliferation and apoptosis, and dysfunctional endothelial repair and angiogenesis, with additional roles for thrombosis, inflammation and changes in metabolism. Although the molecular mechanisms of PH are beginning to be unravelled and numerous potential therapeutic targets have been identified, further research is required to completely elucidate the changes that occur, particularly in non-PAH forms. A greater understanding of the mechanisms of disease and the science behind disease progression should yield improved treatments for PH in the future.

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