Beyond the Lungs: Systemic Manifestations of Pulmonary Arterial Hypertension

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Abstract

Pulmonary arterial hypertension (PAH) is a disease characterized by progressive loss and remodeling of the pulmonary arteries, resulting in right heart failure and death. Until recently, PAH was seen as a disease restricted to the pulmonary circulation. However, there is growing evidence that patients with PAH also exhibit systemic vascular dysfunction, as evidenced by impaired brachial artery flow-mediated dilation, abnormal cerebral blood flow, skeletal myopathy, and intrinsic kidney disease. Although some of these anomalies are partially due to right ventricular insufficiency, recent data support a mechanistic link to the genetic and molecular events behind PAH pathogenesis. This review serves as an introduction to the major systemic findings in PAH and the evidence that supports a common

mechanistic link with PAH pathophysiology. In addition, it discusses recent studies describing morphological changes in systemic vessels and the possible role of bronchopulmonary anastomoses in the development of plexogenic arteriopathy. On the basis of available evidence, we propose a paradigm in which metabolic abnormalities, genetic injury, and systemic vascular dysfunction contribute to systemic manifestations in PAH. This concept not only opens exciting research possibilities but also encourages clinicians to consider extrapulmonary manifestations in their management of patients with PAH.

Keywords: pulmonary hypertension; kidney disease; coronary artery disease; cerebrovascular disease; respiratory muscle dysfunction

Pulmonary arterial hypertension (PAH) is a devastating disease of the pulmonary circulation characterized by progressive loss and obstructive remodeling of the small vessels, leading to right heart failure and

death (1). Historically, PAH has been segregated from systemic vascular disorders, owing to the location of the vascular pathology and the unique biomechanical properties of the pulmonary

vasculature. Vascular pathology in PAH includes a range of lesions characterized by abundant cell growth, neointima formation, fragmentation of the elastic lamina, and vasoconstriction, accompanied

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by muscularization and calcium deposits in the large pulmonary arteries (2, 3). Interestingly, many of these features can also be found in the vascular pathology of common systemic cardiovascular (CV) disorders (e.g., coronary artery disease [CAD], aortic aneurysms, diabetic retinopathy, and hypertensive nephropathy) as well as in certain cancers. For instance, a careful look at plexiform lesions (the histological hallmark of PAH, characterized by endothelial cell [EC] proliferation, luminal occlusion, and disorganized capillary-like channels) reveals some parallels to remodeled peritumoral blood vessels in high-grade glioblastoma multiforme (4). These similarities suggest the presence of common pathophysiological mechanisms that are likely being activated in response to chronic stress and/or injury.

The current paradigm of PAH pathogenesis proposes that the origin of the vascular pathology is multifactorial and involves contributions from inappropriate angiogenesis, metabolic derangements, DNA damage, genetic mutations, and impaired vasoreactivity, among others (5, 6). However, work by our group and others has shown that these abnormalities are not limited to the lungs; in fact, there is evidence of vascular dysfunction in multiple extrapulmonary organs, which has led us to reconsider the concept of PAH as a disease exclusive to the lungs and the right heart.

In this review, we summarize the evidence that links systemic manifestations to PAH. We also discuss the implications of morphological changes to systemic vessels and comment on the possible role of bronchopulmonary anastomoses in the context of plexogenic arteriopathy. We conclude by proposing that PAH should be considered a pulmonary vascular disease with systemic manifestations arising from metabolic abnormalities, genetic injury, and systemic vascular dysfunction. Future studies are needed to determine whether screening for systemic manifestations can serve to risk stratify, treat, and improve clinical outcomes in PAH.

Vascular Dysfunction in the Systemic Circulation of Patients with PAH

The endothelium is a cellular monolayer that covers the inner lining of the entire

circulatory system. Through its strategic position in the vascular wall, the endothelium responds to changes in blood oxygen and nutrient content by producing signals that affect vascular tone, barrier permeability, and recruitment of circulating cells. There is ample evidence for endothelial dysfunction in PAH, as evidenced by impaired angiogenic responses, metabolic changes, and inappropriate activation of inflammatory cascades (6). Indeed, a known marker of endothelial dysfunction in PAH is reduced production of vasodilators (e.g., nitric oxide [NO] and prostaglandins) in lieu of vasoconstrictive factors (e.g., thromboxane A2 and endothelin 1) (7, 8). The majority of research has focused on endothelial dysfunction in the pulmonary circulation without much attention to whether similar abnormalities may be found in the rest of the circulatory system.

Compared with the general population, patients with PAH have a fourfold increased risk of CAD, the leading cause of death in industrialized countries (9). Hospitalization trends between 2001 and 2012 show an increase in patients with PAH with CAD (from 15.6% to 22.3%) that correlates with the presence of CAD risk factors such as diabetes mellitus, obesity, systemic hypertension, and hyperlipidemia (10). Like PAH, the vascular pathology of CAD involves dysfunctional remodeling of the vessel wall, impaired vasoreactivity, luminal obstruction, and inadequate tissue perfusion. A recent study identified that activation of BRD4 (bromodomain protein 4), a transcriptional regulator protein associated with pulmonary artery muscularization and calcification through activation of RUNX2 (Runt-related transcription factor 2) and inflammatory cytokines (11), is involved in promoting CAD in patients with PAH (12). Given its central role in regulating inflammation and DNA repair, two processes known to contribute to PAH pathogenesis, Meloche and colleagues speculate that abnormal BRD4 activity could be a marker of global vascular dysfunction in PAH. The therapeutic value of BRD4 inhibition was validated in preclinical studies (13), and a pilot study of apabetalone (a BRD4 inhibitor) is underway (NCT03655704).

Like the pulmonary circulation, the cerebral circulation is a sophisticated and highly dynamic system in which the ECs respond quickly to changes in blood oxygen

and glucose content, acid–base status, and intravascular volume to preserve cerebral blood flow (CBF). Reduced CBF is a common finding in type 2 diabetes mellitus and heart failure and is associated with cognitive dysfunction, neuroanatomical changes, and exercise intolerance (14). Malenfant and colleagues found that patients with PAH have lower CBF both at rest and with exercise, as evidenced by measures of mean flow velocity in the middle cerebral artery (15). In fact, exercise was associated with a drop in both systemic and cerebral blood oxygen content, further compounding the effects of decreased CBF. Concerning the mechanisms behind the reduced cerebral vascular tone, it has been documented that patients with PAH exhibit reduced cerebrovascular reactivity to blood PCO_2 , which indirectly regulates vascular smooth muscle cell contractility via changes in extracellular pH and by triggering endothelial production of vasoactive compounds such as NO. In addition to reduced cerebrovascular reactivity to PCO_2 , Malenfant and colleagues also discovered that patients with PAH display increased central chemoreceptor sensitivity, which further blunts CBF increase in response to exercise. In addition, in a study of 25 clinically stable patients with PAH, microvascular CBF did not increase in 68% of participants during transition from hypocapnia to hypercapnia compared with healthy control subjects (16). Although both studies focused on the role of PCO_2 , the investigators speculated that decreased NO production by cerebral ECs may also contribute to the blunted vascular tone response, given evidence that sildenafil can improve cerebral vasoreactivity at doses used to treat PAH. Taken together, these findings stress that intrinsic vascular dysfunction in the cerebral circulation might contribute to cognitive impairment and could contribute to the perception of dyspnea and sleep-disordered breathing, two conditions commonly found in PAH (17).

Outside the brain circulation, studies have demonstrated that endothelial dysfunction is also evident in the peripheral circulation of patients with PAH. Hughes and colleagues screened 10 patients with idiopathic pulmonary arterial hypertension (IPAH), 10 of these patients' relatives, and 10 patients with scleroderma–pulmonary arterial hypertension (Scl-PAH) for evidence of systemic endothelial

Figure 1. (A) Slit-lamp photographs show bilaterally dilated port wine–stained episcleral vessels in a 25-year-old patient with heritable pulmonary arterial hypertension (PAH) associated with BMPR2 mutation. The mother, who also had heritable PAH, had the same finding. (B) Nailfold capillaroscopy of patients with scleroderma (Scl). The picture on the left demonstrates nailfold vessels in a patient with Scl without PAH compared with a patient with Scl-PAH (right). Arrows point toward abnormal (left) and normal (right) nailfold capillaries. (C) Sublingual vessels in a healthy subject (left) and a patient with PAH (right).

dysfunction in the brachial artery using flow-mediated vasodilation (FMD), a well-established noninvasive method to measure endothelium-dependent NO production (18). In their assessment, they found significant reductions in brachial artery dilation in 2.7% of patients with IPAH (BMPR2 mutation status unknown) and 6.3% of patients with Scl-PAH.

Interestingly, there was a trend toward a reduced response in family members of the patients with IPAH, suggesting a possible genetic contribution. A larger FMD-based study by Peled and colleagues demonstrated that hyperemic response after brachial artery occlusion was reduced in 54 patients with PAH and that the severity of the impairment directly correlated with disease severity using clinical and hemodynamic parameters (19).

In another study, Wolff and colleagues measured brachial vasoreactivity in 18 patients with PAH undergoing acute vasoreactivity testing with iloprost (20). Compared with control subjects, patients with PAH again demonstrated impaired endothelium-dependent vasodilation that, in contrast to the study by Peled and colleagues, was independent of hemodynamic severity. Interestingly, there was a positive correlation between FMD and the percentage decrease in pulmonary vascular resistance (PVR) with iloprost treatment. Although FMD could be an attractive noninvasive tool to monitor pulmonary vasoreactivity in PAH, more studies are required to determine whether it has any clinical predictive value.

Kidney dysfunction is a common complication of essential hypertension,

heart failure, and metabolic diseases such as diabetes (21). The cardiopulmonary–renal interaction (CPRI) describes a complex reciprocal network of maladaptive neurohormonal activation, oxidative stress, abnormal immune signaling, and cellular damage in which acute or chronic dysfunction of the heart, the lungs, or the kidneys can lead to clinically significant pathology in all three organs (22). The reciprocal nature of CPRI is evident by the high prevalence of chronic kidney disease in patients with PAH (4–46%) and the high prevalence of PAH in patients with chronic kidney disease (16%) (23–25). Interestingly, after adjusting for relevant demographic, functional, laboratory, and hemodynamic parameters, it has been found that kidney function in patients with PAH serves as an independent predictor of poor outcome (26). This suggests that kidney dysfunction in patients with PAH carries a robust prognostic potential that is not solely attributable to the CPRI and could represent a systemic manifestation of PAH itself.

In the setting of low Q, the renal endothelium plays a key role in preserving glomerular blood flow through the production of vasoactive molecules and by acting as a barrier against loss of albumin. Microalbuminuria, defined as urine albumin excretion between 30 and 300 mg/d, is an early marker of systemic endothelial dysfunction that has been associated with multiple CV and metabolic disorders (27–29). However, a study by Nickel and colleagues found that 15–23% of patients with PAH without known kidney disease and traditional CV risk factors demonstrated significant albumin excretion (30). Interestingly, low-grade albuminuria, below the currently defined microalbuminuria threshold of 30 µg/mg, was associated with poor clinical outcome in two independent cohorts of patients with PAH independent of hemodynamic severity. Interestingly, unaffected BMPR2 mutation carriers were found to have elevated excretion of urinary albumin compared with healthy age- and sex-matched control subjects, suggesting a possible contribution of the BMPR2 pathway to albuminuria in patients with PAH. Taken together, these findings reinforce the need for closely monitoring renal function in PAH even in patients with clinically mild disease, but whether routine screening for microalbuminuria has

predictive value or can assist in risk stratification remains to be determined.

The eye is a highly vascularized organ that is sensitive to systemic changes in oxygen and blood flow. Indeed, retinal vascularization abnormalities frequently parallel cardiac, renal, and cerebral vascular alterations in systemic metabolic diseases (31). Interestingly, the presence of abnormal episcleral vessels has been documented in patients with familial PAH with BMPR2 mutations (Figure 1A) (32). Moreover, abnormally dilated episcleral vessels were also found in unaffected carriers before the development of PAH. In a more recent study, Chyou and colleagues used the Multi-Ethnic Study of Atherosclerosis database to show that a higher right ventricular mass and volume by magnetic resonance imaging correlated with a wider diameter in retinal vessels in women than in men, independent of body size, diabetes mellitus, cholesterol, age, and alcohol use (33). Although this study did not involve patients with PAH, it does allow speculation regarding a physiological communication between the retina and the cardiopulmonary system that should be further explored.

Besides the eye, there have been reports of distinctive morphological changes in nailfold capillaries and sublingual vessels (34). Using nailfold capillaroscopy, two studies independently showed reduced capillary density in patients with Scl-PAH and IPAH compared with patients without Scl-PAH and healthy subjects (Figure 1B) (35, 36). Another study quantified blood flow, tortuosity, and curvature of sublingual vessels in 14 healthy control subjects and 26 patients with PAH (Figure 1C) (37). Compared with healthy sex-matched control subjects, patients with PAH had a lower sublingual blood flow index, together with greater tortuosity and curvature. These differences remained significant after controlling for age, sex, and comorbidities such as diabetes and systemic hypertension. Of note, there was no correlation between treatment status, disease severity, and the severity of sublingual vascular parameters in patients with PAH.

It is important to point out that there are currently no data linking the morphological changes seen in the eye, nailfold, and sublingual vasculature to the mechanisms of vascular dysfunction described so far. Nevertheless, it is reasonable to speculate that these lesions might exhibit dysfunctional ECs and

abnormal wall architecture that could be representative of underlying systemic vascular pathology. Dedicated pathological and molecular studies need to be performed to confirm these possibilities.

Metabolic and Endocrine Abnormalities in PAH

Data from the French Pulmonary Hypertension Registry indicate that the prevalence of obesity is increasing in patients with PAH. Compared with the 15% prevalence in the early 2000s (25), a recent report found that the prevalence of obesity in PAH doubled between 2006 and 2016 (38). Obesity is a major health problem in the world and is associated with a high prevalence of metabolic syndrome, a disease entity characterized by insulin resistance (IR), diabetes, and hyperlipidemia. Several studies have shown that patients with IR and diabetes are at increased risk of PAH-related complications. Benson and colleagues found that, compared with patients without diabetes, obese patients with PAH with diabetes mellitus have a lower right ventricular stroke index despite similar mean pulmonary artery pressure and PVR (39). Interestingly, even in the absence of diabetes, IR can be detected in nonobese patients with PAH and is associated with lower survival (40). The mechanism that links IR with PAH has begun to be elucidated using cell- and animal-based models. Mice overexpressing a mutated *Bmpr2* gene develop IR that precedes the development of pulmonary hypertension (PH) and is associated with lower $\dot{V}O_2$ and increased fat deposits in skeletal muscle (41). The mechanistic link in this model was related to defective cytoskeletal regulation of glucocorticoid receptors leading to IR and metabolic syndrome. Similarly, IR was shown to increase the susceptibility to PAH in an apolipoprotein E-deficient mouse fed a high-fat diet (42). In this model, IR was associated with reduced concentrations of the transcription factor PPAR- γ (peroxisome proliferator-activated receptor- γ) in smooth muscle cells that predisposed the animals to develop PH. Treatment of the apolipoprotein E-knockout animals with rosiglitazone (a PPAR- γ agonist used in the treatment of type 2 diabetes) improved insulin sensitivity and led to regression of PH (42). Furthermore, PPAR- γ activation was shown to reduce right ventricular failure

in a rat model of PH by epigenetic and transcriptional regulation related to disrupted lipid metabolism that was associated with pulmonary vascular remodeling and right ventricular failure (43).

Lipids are a major source of energy, key metabolites, and other molecules critical for cell function, but high concentrations can damage blood vessels and heart tissues. High concentrations of circulating free fatty acids can result in large intracellular lipid deposits that trigger production of reactive oxygen species and metabolic dysregulation culminating in cell death, inflammation, and tissue damage (44). Recent studies have shown that circulating free fatty acids are increased nearly twofold in patients with PAH compared with healthy subjects independent of other CV risk factors (45). In line with that, metabolic profiling of plasma from patients with PAH demonstrated that IR strongly correlated with alteration in the lipid metabolic profile (46). The authors found that, similar to atherosclerotic lesions in CAD, plexiform lesions contain proinflammatory lipids (i.e., oxidized low-density lipoprotein) that could serve to promote recruitment of inflammatory cells and disrupt vascular cell function.

Thyroid hormones have a critical role in the regulation of a wide variety of metabolic processes throughout the body, including CV responses to autonomic stimuli and other mediators. Patients with hyperthyroidism can exhibit PH associated with high-output heart failure and increased PVR (47). In line with that, one study reported that the prevalence of elevated pulmonary pressures in hyperthyroid patients estimated by echocardiography ranged from 40% to 94% (48), and reversal of the hyperthyroid state was associated with normalization of pulmonary hemodynamics (49). However, hypothyroidism also appears to be prevalent and is estimated to affect approximately 20–25% of patients with PAH (50, 51). Similarly to hyperthyroidism, hypothyroidism has been linked to EC dysfunction, decreased NO production, and an increase in PVR (52). An additional possible mechanistic link between PAH and hypothyroid disease could be systemic inflammation and autoimmunity, hypoventilation, and impaired cardiac contractility (see Reference 47 for details). Although there is some evidence that thyroid hormone replacement could improve hemodynamics and clinical status, this has yet to be confirmed in larger studies

(53). Thus, even though thyroid disorders were withdrawn from the most current PH classification as a specific entity (now listed in systemic and metabolic disorders 5.2 [54]), the relationship between thyroid diseases and PAH is not entirely understood, and future research on this topic is warranted.

Skeletal and Respiratory Muscle Dysfunction in PAH

The skeletal muscle is highly dependent on a functional capillary network and systemic metabolism. Abnormal systemic vascular and metabolic dysfunction and chronic inflammation all can impact the normal function of the skeletal muscle. Although the typical symptoms of PAH, such as fatigue, shortness of breath, and exercise intolerance, have traditionally been

considered to arise from right heart dysfunction, recent studies have revealed that abnormalities of both skeletal and respiratory musculature contribute to the pathology of PAH (Figure 2). Under physiological circumstances, the skeletal and respiratory muscles comprise approximately 40% of body mass and are responsible for up to 30% of resting $\dot{V}O_2$ (55). The proportion of the Q diverted to respiratory (56) and skeletal muscles increases markedly during maximal exercise, a situation in which the O_2 cost of breathing approaches 10–15% of the total $\dot{V}O_{2max}$ in healthy subjects (57). It is well established that cardiac function is a significant determinant of exercise capacity in patients with PAH with limited cardiac reserve (58, 59). However, many observations have confirmed that exercise limitation in PAH is not merely due to pulmonary hemodynamic impairment.

Indeed, skeletal and respiratory muscle abnormalities such as 1) reduced muscle strength, 2) a switch from type I toward more fatigable type II fibers, 3) altered excitation–contraction coupling, 4) increased muscle protein degradation, 5) decreased capillary density, and 6) impaired mitochondrial function occur independently of the severity of PAH.

Impaired skeletal function has been consistently observed in PAH, including a reduction in volitional (60, 61) and nonvolitional (61, 62) muscle strength and endurance (62–64). Significantly reduced maximal inspiratory and expiratory pressures were also documented (63, 65). Interestingly, in contrast to studies in patients with congestive heart failure and chronic obstructive pulmonary disease (COPD), most studies in PAH documented no changes in whole muscle (61, 63) or fiber cross-sectional areas (61, 66–68). It was also

Figure 2. Features of skeletal and respiratory muscle dysfunction in pulmonary arterial hypertension. Illustration by Patricia Ferrer Beals.

shown that patients with PAH had impaired muscular O₂ use (67, 69–71), partially owing to a significant reduction in skeletal (61, 64, 67) and respiratory muscle capillary density (64). It was shown that capillary rarefaction in patients with PAH was caused by downregulation of microRNA-126, whereas ectopic restoration of microRNA-126 increased capillary density and endurance capacity in a PH animal model (64). Interestingly, the downregulation of microRNA-126 is linked to VEGF (vascular endothelial growth factor) signaling, and it appeared to be specific to PAH muscles, because muscles from patients with COPD had normal microRNA-126 concentrations.

To date, there is no single unifying theory about the pathophysiological background of the systemic myopathy in PAH. As is true of most complex conditions, the mechanisms are most likely to be multifactorial. Skeletal muscles are susceptible to changes in activity and load (72). The limited activities of daily living (73) and the improvement in muscle function after exercise training (74–76) suggest that peripheral muscle inactivity might contribute to this myopathy, which worsens as physical activity declines with disease progression. Moreover, a shift toward fast-twitch muscle fibers is also a critical feature of skeletal muscle disuse that is also documented in congestive heart failure and COPD. However, skeletal muscle abnormalities in PAH have been readily documented in New York Heart Association functional class 2 patients without a sedentary lifestyle (61, 63, 67) and within respiratory muscles exposed to enhanced mechanical load.

The clinician needs to recognize that patients with PAH have a systemic myopathy that presents an increased risk for a functional decline due to loss of muscle function. This is underscored by studies showing that physical training in patients with PAH improves quality of life and functional capacity (76). Thus, clinicians should advise patients to participate in pulmonary rehabilitation programs and engage in regular mild resistance training to counteract the adverse effects of the systemic myopathy in PAH (77).

Bronchopulmonary Anastomoses and Pulmonary Vasculopathy

The lungs receive blood from two sources: the pulmonary arteries and the bronchial

arteries, the latter originating from the aorta and/or intercostal arteries. The bronchial arteries supply oxygenated blood to the airways, lymph nodes, and nerves (78). In lung disorders such as COPD and asthma, bronchial artery hypertrophy characterized by intimal thickening, fenestration, smooth muscle proliferation, and fragmentation of the elastic lamina is a pathological finding linked to reduced blood flow to distal airways and impaired response to bronchodilators (79). It has been reported that 14–75% of patients with PAH have evidence of bronchial artery dilation and hypertrophy detected by computed tomographic scanning, which correlates with the severity of hemodynamic impairment (80). As a follow-up, the authors compared computed tomography and magnetic resonance imaging scans of 18 patients with heritable PAH associated with mutations in the BMPR2 gene against 31 patients with IPAH. BMPR2 mutation carriers had worse hemodynamics and a trend of an increased number of hypertrophied bronchial pulmonary arteries in the BMPR2 mutation carriers compared with noncarriers (81). Even though the authors did not find an increased risk for hemoptysis in BMPR2 carriers, another study found a significant increase in the incidence of hemoptysis in BMPR2 carriers (43.5% vs. 9.5%). BMPR2

mutation carriers were also more likely to harbor anastomoses of the pulmonary arteries with bronchial vessels (defined as singular millimetric fibrovascular lesions or “SiMFis”) (82). The authors performed ink injection studies in a freshly explanted lung of a BMPR2⁺ patient. In this setting, the authors were able to confirm microscopic shunts between pulmonary arteries, veins, and bronchial vessels, which were anatomically linked to atypical plexiform lesions, a hallmark of PAH (Figure 3). Similarly, another group found intrapulmonary bronchopulmonary anastomotic pathways in lung tissue from five adult subjects who had died of complications associated with IPAH. Using serial sectioning and three-dimensional reconstruction to analyze areas involved by plexiform lesions, the authors found conclusive evidence of patent intrapulmonary bronchopulmonary anastomotic pathways connected to dilated and congested bronchial veins in all five subjects (83).

Given the lack of biopsy material in early disease and the unpredictable distribution of lesions, little is currently known about the pathological mechanisms that drive the formation of shunts between the bronchial and pulmonary circulation, whether there is reversal with a response to therapy or if these shunts are a complication of PAH. Possible contributors to bronchial

Figure 3. Plexiform lesion in the lungs of a patient with heritable pulmonary arterial hypertension (positive for BMPR2 mutation). The overview depicts a pulmonary artery of subsegmental level (left) with its adjacent airway (right); the magnification of the selected area (black square) shows a plexiform lesion that appears to connect to a bronchial artery within the wall of the bronchiole. Scale bar, 1,000 μ m.

The Microbiome and Systemic Inflammation

Pulmonary vascular inflammation has been recognized as a key event in PAH. (For comprehensive reviews, *see* References 84 and 85). Although there is evidence of proinflammatory cytokine production within vascular lesions, there is evidence that circulating concentrations of inflammatory proteins are also elevated in patients with PAH, suggesting the possibility that inflammatory signals could also be coming from the systemic circulation (86). Systemic inflammation can be triggered by bacterial translocation or translocation of bacterial byproducts from the gastrointestinal tract into the systemic circulation (87). A recent study showed that patients with PAH have a high correlation of macrophage activation markers (such as soluble CD14 [cluster of differentiation 14] and Toll-like receptor 4) and circulating LPS concentrations, suggesting chronic bacterial translocation (88). Interestingly, after initiation of PAH-targeted therapy and improvement of right-sided hemodynamics, the circulatory LPS load decreased, underlining the importance of right heart hemodynamics in enteric congestion and intestinal barrier function. Future clinical research is needed to substantiate these hypothesis-generating findings.

Besides proinflammatory properties, the commensal human microbiome can influence pulmonary vascular smooth muscle relaxation and proliferation by alterations in NO and hydrogen sulfide signaling and production (89). Ingested nitrate undergoes enzymatic and nonenzymatic reactions to produce NO, which is rapidly absorbed in the proximal gastrointestinal tract and systemically circulated, whereby they can instigate salutary NO signaling responses. Numerous studies have demonstrated that an intact, viable oral microbiome is necessary to potentiate dose-dependent improvements in endothelial dysfunction (90) and inflammation (91). Although more studies need to be conducted, it is attractive to think that pharmacological interventions targeting the microbiome could have a role in PAH treatment.

Conclusions

Abnormal vascular responses and morphological changes in systemic vessels are part of the clinical picture of PAH

Figure 4. Proposed model for mechanisms of pulmonary and systemic vascular manifestations in pulmonary arterial hypertension. Illustration by Patricia Ferrer Beals. CBF = cerebral blood flow; FFA = free fatty acids; FMD = flow-mediated vasodilation; RV = right ventricle.

artery involvement are local inflammation, altered hemodynamics, and bronchial artery EC dysfunction. Research on imaging tools to capture the number and

location of these shunts might provide an opportunity to identify patients with PAH at high risk of lung hemorrhage and hemoptysis.

and can adversely affect the functional status of these patients. We propose that PAH is a pulmonary disease with systemic manifestations that arise from multiple factors, including abnormal endothelial responses, metabolic dysregulation, and inflammation (Figure 4).

Even though extrapulmonary manifestations in PAH are often clinically subtle, they could have a significant impact on patient outcome. Future research may shed more light on the molecular underpinnings of extrapulmonary morbidities in PAH and lead to tailored

interventions. Until then, structured physical exercise and controlling modifiable CV risk factors will be essential measures in the treatment of PAH. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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