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Review article

A review of cardio-pulmonary microvascular dysfunction in pulmonary hypertension

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ABSTRACT

Microvascular dysfunction progressing to pulmonary hypertension can be a primary cause of right ventricular failure or a secondary cause because of an underlying systemic illness. Little is known regarding the etiology and epidemiology of coronary microvascular dysfunction in pulmonary hypertension. Despite this limitation, its presence has been described in patients with pulmonary hypertension. This review focuses on the pathogenesis of cardiac and pulmonary microvascular dysfunction in pulmonary hypertension. Additionally, this review provides a contemporary assessment on the diagnosis and treatment of microvascular dysfunction in patients in pulmonary hypertension. This topic is important to raise awareness of microvascular dysfunction in the coronary and pulmonary circulation, so that future studies will investigate its impact on the pulmonary hypertension patient cohort.

1. Introduction

Pulmonary hypertension (PH) is characterized by pulmonary vascular remodeling with a corresponding increase in pulmonary vascular resistance (PVR). Progressive elevation in PVR results in increased right ventricular (RV) afterload and RV remodeling. The RV remodeling is eventually maladaptive and leads to RV failure (RVF). Uncoupling of the RV and pulmonary artery (PA) occurs when the pulmonary vasculature remodels to the point where the RV can no longer support its respective afterload [1–3].

Endothelial dysfunction is well described in the pathogenesis of PH with respect to pulmonary endothelial vasculature. The role of endothelin-1, prostacyclin, nitric oxide (NO), thromboxane, vascular endothelial growth factor pathways are described in the literature as mediators of PH and are important regulators of pulmonary endothelium with respect to pulmonary microvascular dysfunction (PMD) [4]. Coronary microvascular dysfunction (CMD) is defined by structural and functional abnormalities of coronary microvasculature. Its mechanisms

Abbreviations: ACE, angiotensin-converting enzyme; ACVRL1, activin receptor-like kinase-1; BMPR2, bone morphogenetic protein receptor type 2; BMP9/10, bone morphogenetic protein-9/-10; CAD, coronary artery disease; CBF, coronary blood flow; CCB, calcium channel blocker; CFR, coronary flow reserve; CMD, coronary microvascular dysfunction; CFVR, coronary flow velocity reserve; cMRI, cardiac magnetic resonance imaging; CT, computed tomography; CTCA, coronary CT angiography; CTEPH, chronic thromboembolic pulmonary hypertension; ENG, endoglin; HIF, hypoxia-inducible factor; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; ICA, invasive coronary angiography; ILD, interstitial lung disease; LAD, left anterior descending artery;; LV, left ventricle; LVF, left ventricular failure; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; MVR, microvascular resistance; NO, nitric oxide; OSA/OHVS, obstructive sleep apnea/obesity hypoventilation syndrome; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PDGF, platelet-derived growth factor; PEA, pulmonary endarterectomy; PET, Positron emission tomography; PH, pulmonary hypertension; PMD, pulmonary microvascular dysfunction; PVOD, pulmonary veno occlusive disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle; RVF, right ventricular failure; SCD, sickle cell disease; SPECT, single-photon emission computed tomography; TGF-B, transforming growth factor-B; TTE, transthoracic echocardiography; VEGF, vascular endothelial growth factor.

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are heterogenous and CMD is present within various cardiovascular diseases [5].

Little is known on the role of CMD in RV dysfunction. Despite this, CMD likely plays an important role in the development of RVF and uncoupling of the RV and PA in PH patients. This review paper will focus on endothelial dysfunction from the standpoints of pulmonary and coronary vasculature (Fig. 1).

2. Pathophysiology of microcirculatory dysfunction

2.1. Coronary microvascular dysfunction

Coronary blood flow is maintained by epicardial arteries, prearterioles, and arterioles. Acute coronary syndromes were thought to develop primarily by large vessel epicardial arterial atherosclerosis, plaque rupture, and thrombosis; leading to large territory ischemia and infarction [5]. Coronary microvascular disease (CMD) occurs by pathological changes in the arterioles, causing decreased ability to vasodilate and perfuse microvascular territories, analogous to the Glagov phenomenon [5,6]. This occurs both through morphologic changes in smooth muscle and functional changes in endothelial cells. As the microcirculation progressively stiffens, it can no longer relax to accommodate blood flow during periods of greater oxygen demand [5].

When exposed to factors that cause microvascular dysfunction, arterioles become increasingly contractile with impaired relaxation. There is an upregulation of both vasoconstrictive mechanisms and resistance to vasodilatory mechanisms [7]. In response to injury, smooth muscle cells undergo phenotypic changes. This alters them from mature cells that control contraction and relaxation to synthetic cells that causes them to proliferate and migrate. This proliferation and migration of immature cells results in hypertrophy [8]. The impaired coronary microvascular flow eventually leads to concentric hypertrophy and diastolic dysfunction in the left ventricle (LV) [8].

2.2. Pulmonary microvascular dysfunction

PMD may develop by molecular mechanisms similar to CMD, as both are due to pathology within vascular smooth muscle and endothelium. Coronary microvasculature is made up of prearterioles and arterioles, where metabolic regulation of blood flow occurs, and which undergo deleterious vascular remodeling in response to stress. Pulmonary arterial hypertension (PAH) is known to occur by vascular impairments in relaxation and increased contraction and vascular resistance [9]. Similar to CMD, PAH results in an upregulation of vasoconstrictive molecules resulting in a high-pressure environment [5,9]. In PAH, the underlying cause of endothelial dysfunction that leads to an imbalance toward vasoconstriction is idiopathic, nevertheless the pathophysiological results are similar to those that occur in CMD [9].

Mutations in the TGF-β (transforming growth factor-beta) signaling pathway account for most familial cases of PAH. Errors in this pathway lead to overproduction of pro-growth signaling pathways causing endothelial cell proliferation [10]. Mutation of BMPRII receptor favors hyperproliferation and an endothelial-to-mesenchymal cellular transition that resembles the phenotypic cellular change that occurs in CMD [10,11]. These mutations in PAH favor vascular smooth muscle and endothelial proliferation which progressively narrows the vessels, leading to increased PA pressure [10]. PAH also features characteristic plexiform lesions, which are organized vascular structures with cellular upregulation of MMP9 and NOTCH pathways that respond to TGF-β signaling [12]. A culmination of multiple factors favoring vasoconstriction, endothelial dysfunction, and downregulation of vasodilatory counteraction leads to progressive PA resistance and afterload on the RV [9]. As seen in chronic lung diseases associated PH, chronic hypoxia activates HIF-1a (hypoxia-inducible factor-1 a) and TGF-B pathways to pulmonary artery smooth muscle proliferation and vascular remodeling [13].

2.3. PMD and CMD in relation to PAH

It is likely that there is interplay between CMD and PAH, as PAH patients have reduced coronary flow reserve (CFR) and lower myocardial perfusion on cardiac magnetic resonance (cMRI) testing [14]. There is also evidence that patients with PAH have concomitant CMD affecting both ventricles [15]. Chronic hypoxia can also lead to systemic inflammation, precipitating microvascular dysfunction in the coronary vasculature [16].

As resistance increases in the PA, RV afterload increases, prompting the RV to undergo remodeling as well. This occurs regardless of the etiology of the PH. Patients with PAH have been shown to have RV diastolic dysfunction likely secondary to this hypertrophic remodeling [17]. Initially the RV-PA system can adapt and preserve efficient blood flow through the ventricle and into the lungs, but as PA load increases the system uncouples and becomes less efficient, leading to first diastolic then systolic RVF [18,19]. CMD, through diastolic dysfunction of the LV, can also lead to group 2 PH and RV dysfunction [8]; high left-sided pressures cause pulmonary vascular congestion, increased pulmonary venous pressure, and hypoxic vasoconstriction and endothelial dysfunction in the pulmonary vascular system [20]. RV dysfunction in the two entities (PAH and left sided heart failure associated with PH) does have distinct phenotypes. Whereas RV dilation is more prominent in pure PAH and can be used to distinguish pre-capillary and post-capillary PH; left atrial dilation is more prominent in heart failure with preserved ejection fraction (HFpEF) [20].

CMD and PMD share mechanisms of disease (Table 1), in that both CMD and PAH develop through endothelial dysfunction and progressive vasoconstriction. Increasing afterload leads to progressive RV concentric hypertrophy and RV diastolic dysfunction. In both PAH and coronary artery disease, RV diastolic dysfunction precedes RV systolic failure [20]. CMD can manifest as HFpEF, PH due to left heart failure, and subsequent RV dysfunction. Likewise, PAH develops RV failure from increasing afterload, and thus both present with similar RV dysfunction. RVF can be seen as a possible shared pathophysiologic endpoint of both CMD and PMD [21].

In CMD, vascular tone is largely controlled by calcium. Ion channels contribute a source of activator calcium which determines vascular tone and regulates the membrane potential, thereby determining the open-state probability of voltage gated Ca^{2+} channels. Vasoconstrictor molecules like norephinephrine, endothelin, angiotensin II, and 5-HT act to increase open-state probability of voltage-gated calcium channels; molecules like isoproterenol, adenosine, prostacyclins counteract those

Highlights

- Pulmonary hypertension and right ventricular failure are downstream sequele of microvascular dysfunction
- Both coronary and pulmonary microvascular dysfunction are present in patients with pulmonary hypertension
- Coronary and pulmonary microvascular dysfunction may be involved in the pathogenesis of pulmonary artery and right venticular uncoupling
- More investigation is needed to diagnose and treat microvascular dysnfunction in pulmonary hypertension patients

Fig. 1. Highlights of the review paper.

Table 1
Comparison of molecular mechanisms and phenotypic changes between CMD and PMD.

	CMD	PMD
Molecular mechanisms	• Nitrate resistance impairing vasodilation due to [7]: o reduced production of cGMP, • Vasoconstriction by upregulation of [7]: o norepinephrine o endothelin o angiotensin-II o 5-HT o alteration of voltage-gated Ca2+ channels	• PAH has increased vasoconstriction [9]: o ↓ NO synthase activity o ↓ prostacyclins
Phenotypic changes	• Impaired vasodilation secondary to [8]: o arteriole smooth muscle hypertrophy o collagen deposition o intimal thickening • Smooth muscle cells undergo phenotypic changes in response to injury [10]: o Changes in cellular type and function to promote remodeling	• In PAH, the endothelial cells respond to increases in PA pressure by [9]: o releasing molecules such as: platelet derived growth factor TGF-β that stimulate smooth muscle proliferation o further stiffening the vessels and increasing resistance • Mutations in the TGF-β family lead to overproduction of pro-growth signaling pathways causing endothelial cell proliferation [10] o Genetic mutations ex: ▪ BMPRII receptor ▪ ACVRL1 ▪ Smads ▪ BMP9 ▪ BMP10 • Proliferative factors that are independently upregulated in PAH [9]: o endothelin-1 o PDGF o ACE o VEGF o VEGFR2 • Develop characteristic plexiform lesions [9]

Legend: CMD, coronary microvascular dysfunction; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PMD, pulmonary microvascular dysfunction.

effects. NO decreases the activity of voltage gated calcium channels to also favor vasodilation [7].

In PMD, molecular mechanisms that maintain low arterial resistance include prostacyclins and NO; phosphodiesterases act to degrade NO. Patients with PAH have reduced NO synthase activity, decreased prostacyclins, and increased vasoconstriction by thromboxane A2 and endothelin [9]. Mutations in the negative regulatory limb of the TGF-β super family favor hyperproliferation. Thus, BMP9, a ligand that serves as an agonist of the BMPRII receptor, can circulate and protect endothelial cells from excessive proliferation. Mutation of the BMPR2 receptor then favors hyperproliferation and an endothelial-to-mesenchymal cellular transition that resembles the phenotypic cellular change that occurs in CMD [10,11].

2.4. Diastolic dysfunction and microvascular dysfunction in PH

Patients with PAH have been shown to have RV diastolic dysfunction [22,23]. Suggested mechanisms of diastolic dysfunction in PAH patients included increased sarcomere stiffness and increased RV collagen deposition that is part of the compensatory mechanism of elevated pulmonary vascular pressures resulting in RV hypertrophy [22]. In LV diastolic dysfunction, disruption of endothelial cell Sirtuin 3 (SIRT3) expression has adverse effects on glycolytic metabolism and impairment of angiogenesis [24]. This leads to cardiomyocyte hypoxia, cardiac microvascular rarefaction, and myocardial fibrosis leading to diastolic dysfunction. This process is not established RV diastolic dysfunction but does provide an intriguing hypothesis for future studies. LV diastolic dysfunction has been reported in association with Group 1 and 4 PAH, as a potential result of RV pressure overload which causes impaired LV function [25]. It is worthwhile to entertain the possibility that the systemic microvascular dysfunction, as seen in connective tissue diseases, may non-selectively affect both ventricles causing change in ventricular structure.

LV diastolic dysfunction is classified as a cause of group 2 PH, the development of RVF may also worsen LV diastolic dysfunction and worsen outcomes in patients with defined combined post-capillary and pre-capillary PH [23,26]. Multiple pathologies result in diastolic dysfunction and it can be seen in heart failure in preserved or reduced ejection fraction. PH develops in response to a cumulation of pulmonary vascular congestion, chronic hypoxia and inflammation, and age related vascular dysfunction associated with coronary artery disease [26].

3. CMD and PMD across WHO groups

3.1. On coronary microvascular dysfunction

The influence of CMD in PH is unclear. While it has been observed that systemic effects of chronic inflammatory conditions can contribute to CMD, there is no research to date looking at CMD related to systemic effects from PH [5]. In theory, several of the disease processes for PMD may have effects on the coronary microvasculature. For example, chronic intermittent hypoxia is known to create systemic inflammation which triggers microvascular changes in the coronary arteries [16]. It is possible that hypoxia from PH can contribute to PMD (for example in group 3 PH) and may also lead to CMD through similar mechanisms. It is important to understand any direct cardiac effects, such as CMD, that potentiate RVF in PH patients because of its associated morbidity and mortality.

CMD in group 2 PH is of particular interest. There is a unique relationship between CMD, PMD, cardiac function and PH that is not seen in the other groups. As described in literature, CMD can cause LV failure (LVF) [27]. One could theorize that the entire heart (both left and right) may be affected equally by CMD and that PH serves as a secondary stressor that exacerbates RVF. However, it is also possible that the left heart may be impacted by CMD first, which can then cause PH. This could trigger inflammatory pathways of CMD in the RV, leading to eventual RVF.

3.2. On PMD

There are similarities and differences in histopathology and molecular mechanisms of PMD within the various PH WHO group

classifications. Table 2 summarizes key differences amongst these different subtypes.

3.2.1. Group 1 – pulmonary arterial hypertension

Data exploring the mechanisms underlying the vascular remodeling in PAH have identified several pathways. Common endpoints like impaired NO signaling or endothelial dysfunction drive the progression of obliterative vascular remodeling [28]. In the case of hereditary PAH some theorize that genetic variations (i.e. BMPR2, ACVRL-1, ENG) predispose patients to these insults [12]. Endothelial damage tends to be progressive. In advanced PAH, hyperproliferative and apoptosis resistant endothelial cells form complex whorls called plexiform lesions - one of the hallmark histologic findings of PAH [29].

Chronic hypoxia appears to be a driver of the pathways mentioned above. Animal models with gene knockouts that code for HIF-1a and 2a have shown blunted hemodynamic compromise related to RVF when exposed to states of chronic hypoxia. Subsequent animal studies of PAH show that inhibition of HIF-a and its associated axis can actually improve RV and hemodynamic function [30].

Table 2
PMD in PH patients amongst the different WHO groups.

WHO group	Observed histopathologic changes	Pathophysiology/molecular pathway
Group 1	• Muscularization of small arteries [12]. • Increased intimal and medial thickness of venous microcirculation [12]. • Plexiform lesions [29].	• Endothelial dysfunction and impaired NO signaling [22]. • Vascular obliteration due to HIF pathway [30].
Group 2	• Hemangiomatosis like changes[a] [33,45].	• ↑ hydrostatic pressure causing release of factors causing [33]: • ↑ oxidative stress • Leukocyte infiltration • Fibrotic changes.
Group 3	• ↑ media thickness and muscularization of non-muscular arteries [13,46].	• HIF pathway [13]. • Direct toxic effect (i.e. smoking) [13]. • Genetic predisposition for smooth muscle hypertrophy and endothelial hyperplasia [13].
Group 4	• Hemangiomatosis like changes[a] [33]. • ↑ small vessel muscularization (like those in group 2 PH) [33]. • Plexiform lesions [47].	• Shunting between systemic and pulmonary vasculature [48]. • Endothelial and platelet derived factors opening bronchopulmonary arterial anastomosis [48].
Group 5	SCD	SCD [49]:
	• Findings as described in PAH, CTEPH, and Group 3 PH [49].	• Impaired NO metabolism and endothelial dysfunction from hemolysis • Hypercoagulability leading to thrombi in both the large and micro vasculature. • HIF pathways
	SAPH	SAPH [44]:
	• Granulomas with invasion into vessels • Venous changes similar to PVOD [50]. • Plexiform lesions [51].	• Direct endothelial damage and obstruction from granulomas. • Impaired NO release • ↑ endothelin 1 levels. • ↑ vasoconstriction and cell proliferation. • HIF pathway from parenchymal fibrosis. • Hypercoagulable state with thrombotic obstruction.

Legend: CTEPH, chronic thromboembolic pulmonary hypertension; HIF, hypoxic inducible factor; NO, nitric oxide; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVOD, pulmonary veno-occlusive disease; SAPH, Sarcoid associated PH; SCD, sickle cell disease.

[a] Intimal thickening and medial hypertrophy of pulmonary vasculature.

Variability in disease location and microvascular pathology may play a role in the inconsistent treatment responses to existing therapies. Better characterization of PMD in PH can provide potential new therapeutic targets aimed at limiting endothelial dysfunction and both smooth muscle and adventitial fibroblast proliferation which have been shown to drive RVF [31].

3.2.2. Group 2 – PH due to left heart disease

Group 2 PH is the most common form of PH and it is defined by the presence of post capillary PH on RHC in the setting of known left heart disease [32]. Microvascular dysfunction plays a role in group 2 PH, beyond its known effects on coronary microvasculature. Studies specifically focused on PH in patients with HFpEF have shown that PMD is a potential risk factor for severe disease along with other comorbid conditions like chronic obstructive pulmonary disease (COPD) or atrial fibrillation [33].

In PH due to HF, both reduced ejection fraction (HFrEF) and HFpEF, the primary driver of PH is impaired LV relaxation and increased filling pressures which leads to stress failure in the post capillary pulmonary vascular system. Even transient periods of pulmonary edema can contribute to the characteristic small vessel muscularization and endothelial dysfunction seen in Group 2 PH [33]. Chronic hypoxia from heart failure may serve as an additional driver of the PMD seen in Group 2 PH through mechanisms described below in Group 3 PH.

3.2.3. Group 3 – PH due to chronic lung diseases

Many of the disease pathways in group 3 PH involve chronic states of hypoxia. Much of the literature describing mechanisms of microvascular changes comes from models that simulate hypoxia [13]. Of particular importance are the HIF pathways which serve as regulators of oxygen homeostasis. Expression of these factors in response to hypoxia upregulate VEGF expression, driving angiogenesis. This signals a shift to anaerobic metabolism resulting in mitochondrial induced endothelial damage [13]. In rat models of chronic hypoxia related PH, restriction of the HIF pathways through inhibition of mitochondrial fission shows significant improvement in RV function and hemodynamics [13].

Patients with PH due to chronic obstructive pulmonary disease (COPD-PH) showed that microvascular changes correlated clinically with PH severity. The pathogenesis includes: reduced parenchymal loss and associated alveolar hypoxia; chronic hypoxemia and hypercapnia as a result of pulmonary vascular bed destruction; effects of air-trapping and hyperinflation; polycythemia; and inflammation-induced vascular remodeling secondary to smoking [34]. Patients with severe COPD-PH had more microvascular muscularization, intimal fibrosis, and medial hypertrophy than those with moderate COPD-PH; as measured by a modified version of the vascular assessment score for PH in animal models [35]. The vascular lesions morphologically resemble those in idiopathic PAH [36].

Microvascular changes are not necessarily isolated to areas of lung impacted by chronic lung disease. In studies of PH due to pulmonary fibrosis, regions of microvascular change were independent of those with parenchymal disease [13]. This suggests that there are likely organ wide changes driven by some of the factors as listed above.

3.2.4. Group 4 – specifically on PH due to chronic thromboembolic pulmonary hypertension (CTEPH)

CTEPH is characterized by PH due to thromboembolic disease in small and large pulmonary arteries. PMD in CTEPH is a well-recognized disease entity as it contributes to poor postoperative outcomes for pulmonary endarterectomy (PEA) [37]. In CTEPH, small vessel thrombotic obstruction may result in microvascular disease due to altered blood flow. Microvasculature distal to sites of obstruction shows changes typical for PH arteriopathy. These changes are seen predominantly in small vessels distal to sites of obstruction but are present even in non-obstructed vessels which suggests a more systemic effect [38].

Certain patients with CTEPH may be eligible for definitive treatment

with PEA. Unfortunately, a subgroup of patients has treatment refractory disease even after PEA and PMD appears to be a significant factor of poor postoperative outcomes in these patients. Histologic analysis of transplanted lung tissue from patients who had CTEPH refractory to PEA showed more significant microvascular changes [39].

3.2.5. Group 5 with emphasis on sarcoidosis and sickle cell disease

PMD in group 5 PH is difficult to characterize because of the range of diseases that are included in this group and treatment responses in PAH therapy are variable. This section will focus on PH patients with sickle cell disease (SCD) and sarcoidosis (SCD-PH).

The pathogenesis of SCD-PH overlaps with other PH groups, most notably CTEPH [40]. Particularly in patients with SC genotype, pulmonary thromboembolic disease is a major contributor to precapillary PH [40]. This seems driven by local factors as the prevalence of DVT is relatively low [32]. While PH in SCD does not have any targeted treatments there is some data suggesting promise with therapies for PAH [40] in addition to evaluating new therapeutics that target impaired NO synthesis via cGMP [41].

Sarcoid associated PH (SAPH) is also multifactorial with many disease features that mirror other groups of PH. SAPH is present in up to 74 % of patients with severe sarcoidosis and studies exploring PH targeted therapies have not shown significant benefit [42,43]. The role of left heart disease and post capillary PH in SAPH is still not completely understood. Limited studies do show that the presence of cardiac sarcoidosis may be higher than previously reported, which may drive some of the pathways outlined above in Group 2 PH [44]. Additionally, in patients with cardiac sarcoid, SAPH tends to improve with treatment of heart disease [42].

4. Diagnosis of microvascular dysfunction

4.1. Rationale

Like the LV, the RV can be affected by structural and functional abnormalities of the coronary microvasculature. This involves the epicardial, microvascular endothelial, and nonendothelial dysfunction that limits myocardial perfusion [52]. Potential mechanisms have been identified that include enhanced coronary vasoconstrictive reactivity at the microvascular level, blunted endothelium-dependent and independent coronary vasodilator ability, and increased coronary microvascular resistance [5]. This can occur with or without CAD. Similar inflammatory markers have been associated with coronary and PMD [53,54]. As pulmonary vascular remodeling progresses, downstream effects of RV dysfunction and inflammation likely interplay into the development of RV-PA uncoupling [20]. Similar inflammatory processes have been proposed in ventricular-arterial uncoupling in cardiac disease and heart failure [55]. The importance of reviewing how CMD is diagnosed is that these diagnostic modalities may offer prognostic value in PH patents and may reveal a need for timely intervention.

4.2. Cardiovascular microvascular dysfunction

While non-invasive testing, as listed in Table 3, is helpful in the work up of CMD, invasive testing is used to establish the diagnosis. Similar characteristics predispose to CMD as obstructive CAD (i.e. atherosclerosis, age, hypertension, diabetes, dyslipidemia, and chronic inflammatory disease) which make the diagnosis challenging. CMD is more prevalent in middle aged women. Clinically, CMD should be suspected in patients with signs and symptoms of myocardial ischemia with known non-obstructed coronary arteries. However, it should be noted that regardless of clinically significant CAD, CMD may be present.

4.3. Noninvasive testing modalities

4.3.1. Positron emission tomography (PET)

PET is the most commonly used assessment of myocardial blood flow (MBF) by using tracers (i.e. O-15 water, N-13 ammonia, or Rubidium-82) to obtain myocardial perfusion imaging and is the gold standard for noninvasive assessment of CMD [56]. It also allows quantification of global perfusion reserve. PET scan provides a comprehensive evaluation of coronary blood flow (CBF) and CFR. Specifically, using F-18 label tracers in PET/computed tomography has proved useful for detecting coronary plaques with high risk features such as microcalcifications to aid in risk stratification of coronary artery plaques [5,57,58]. In patients with non-ischemic cardiomyopathy, the use of PET has demonstrated inverse correlation between degrees of LV thickness as a predictor of existing CMD [56]. Its benefit is that it allows all coronary territories to be evaluated at the same time. However, it is time consuming, costly, and results in radiation exposure [59].

Table 3
Diagnostic modalities used in the evaluation of CMD.

Diagnostic modality	Measures	Advantages	Disadvantages	Considerations
PET	Global perfusion reserve MBF CFR	Can identify CAD and CMD Gold standard Not limited by renal function	Radiation exposure Time consuming Costly Limited availability	Can be combined with CT Most useful in absence of obstructive epicardial stenosis
TTE	CFVR of LAD	Allows simultaneous measurement of regional wall motion dysfunction Readily available Inexpensive No radiation	Limited assessment of vasodilatory microvascular function Only assesses LAD User dependent	Very limited data available on CMD assessment Applicability limited to patients without epicardial stenosis
cMRI	MBF CFR	Evaluates all coronary territories simultaneously Can be used in obese patients No radiation	Timely Costly Limited by renal function	Also provides diagnostic evaluation of cardiac function
Cardiac CT	MBF MPR	Can evaluate for coronary territories simultaneously Assesses both epicardial and microvascular disease at same time	Radiation exposure Limited by renal function May overestimate MBF	Can be combined with PET Used in CAD and CMD workup
SPECT	MBF	Readily available Low cost	Significant radiation exposure Limited image quality in CMD due to pharmacokinetics of radiotracers	May be able to provide measurements of myocardial flow that is difficult for PET New high sensitivity cameras and radiotracers emerging to improve MBF quantification

Legend: CAD, coronary artery disease; CMD, coronary microvascular dysfunction; cMRI, cardiac magnetic resonance imaging; CFVR, coronary flow velocity reserve CT, computed tomography; LAD, left anterior descending artery; MBF, myocardial blood flow; MPR, myocardial perfusion reserve; PET, positron emission tomography; SPECT, single-photon emission computed tomography; TTE, transthoracic echocardiography.

4.3.2. Transthoracic echocardiography (TTE)

TTE with pulse wave doppler of LAD artery, at rest and after dipyridamole, allows measurement for coronary flow velocity reserve (CFVR). If there is no epicardial flow limitation, this is used as a ratio to measure coronary microvascular function [59]. Typically, this helps serves as an independent risk stratification method for patients, outside the observation of regional dysfunction during dobutamine stress echo [59]. The benefits of TTE are that it is readily available, inexpensive, and offers no radiation exposure. Limitations of TTE include a restricted assessment of vasodilatory microvascular function and are mostly limited to the LAD region in determining CMD [59].

4.3.3. Cardiac magnetic resonance imaging (cMRI)

cMRI is used with vasodilator stress (i.e. intravenous adenosine or regadenoson) and provides diagnostic and prognostic information in setting of CMD. cMRI can also describe MBF and CRF using resting and stress perfusion quantification like PET. It evaluates all coronary territories at the same time with no radiation exposure [59]. Oxygen-sensitive cMRI, otherwise known as blood oxygen level-dependent cMRI has been used to identify reduced myocardial oxygenation of the LV, implying CMD, in patients with confirmed non-severe pre-capillary PH [5,37].

4.3.4. Computed tomography (CT)

Coronary CT angiography (CTCA) is becoming more popular for functional testing [59]. It allows similar quantitative assessment that MRI offers through MBF and myocardial perfusion reserve (MPR), but evidence is currently limited in comparison. Its limitation includes both significant radiation exposure and the need for further investigation in CMD. Combined CT perfusion and CTCA is the only non-invasive technique, aside from PET, that allows exclusion of epicardial CAD and assessment of microvascular vasodilatory function with one diagnostic tool.

4.3.5. Single-photon emission computed tomography (SPECT)

SPECT uses perfusion radiotracers to assess quantify MBF related to CMD. Largely felt to be inferior to PET imaging, but could provide clinically relevant measurements of myocardial flow reserve in sites that PET is not able to assess [60,61]. New modifications using high-sensitivity cardiac cameras during SPECT imaging may improve quantification of coronary flow in CMD, but further qualitative studies are needed.

4.3.6. Limitations of non-invasive modalities

While noninvasive testing provides evidence suggesting CMD, obstructive CAD must be ruled out to confirm CMD diagnosis via coronary CT angiography or invasive coronary angiography [59,62]. Vasodilators used in the above modalities (i.e. dipyridamole, regadenoson, or adenosine) assess vasodilator capacity but do not directly access coronary endothelial function or coronary spasm. Only invasive assessment can distinguish the different subtypes of CMD. Limited studies have explored CMD specifically in PH patients.

4.3.6.1. Invasive testing. CBF is driven by the pressure difference between that aorta and capillary bed which is regulated by physical and neural factors that influence the microcirculation [52]. Pathways commonly tested during cardiac catheterization include (1) non-endothelium dependent using adenosine to measure CFR [<2.5 CFR] and (2) endothelium dependent using acetylcholine to measure coronary blood flow [<50 %].

Coronary reactivity testing, with adenosine or an analog, is required to diagnose CMD. Invasive coronary angiography (ICA) can exclude obstructive CAD. In setting of obstructive CAD, slow contrast movement and failure to restore optimal myocardial perfusion (no-reflow phenomenon) in the setting of chest pain and ischemic ECG changes, immediately post-stenting, implies CMD versus coronary emboli from stent placement. Approaches for diagnosis of CMD during ICA, include CFR and microvascular resistance (MVR) measurements by intracoronary doppler or thermodilution and acetylcholine spasm provocation testing [59]. Coronary microvessels are not visible angiographically and testing is predicated on indirect signals of microvascular function. Microvascular vasodilatory capacity is assessed by measurement of CFR and/or MVR during rest and pharmacologically induced hyperemia using intracoronary administered vasodilators. It is important to note CFR can only demonstrate CMD in the absence of obstructive CAD. Microvascular spasm diagnosis is focused on patient symptoms and ECG changes during spasm provocation testing [59]. Currently there are no methods of evaluating CMD of the RV through ICA and more studies are needed to validate the diagnosis of CMD in PH associated RVF.

4.3.6.2. Pulmonary microvascular dysfunction. PMD is best understood in the context of CTEPH from a diagnostic and interventional standpoint. CTEPH is classically screened for using non-invasive (i.e. TTE and V/Q scan) and confirmed on RHC. Location and extent of pulmonary microvascular and macrovascular abnormalities determines interventional and therapeutic approach. More pronounced microvascular disease contributes to higher pre-operative PVR, which is associated with greater postoperative mortality [48].

4.3.6.3. Noninvasive testing modalities. Noninvasive methods are lacking in substantial investigation for PMD. One study in COPD patients used assessed regional pulmonary parenchymal perfusion by MRI to quantify pulmonary blood flow and correlated these findings with global lung perfusion and diffusing capacity for carbon monoxide [63]. While this is not validated to investigate PMD, this is promising for future studies using MRI to investigate pulmonary vascular disease.

4.3.6.4. Invasive testing. Animal models in CTEPH have been used to measure the total pulmonary resistance index (TPRI) in conjunction with biomarkers (i.e. human et-1, il-6, and CRP levels) to reflect PMD [64]. Upon re-establishing pulmonary blood flow, this study demonstrated improved PMD through improvement in transpulmonary resistance (TPR). Another small study, using baboons, revealed that pulmonary flow reserve and pulmonary index of microcirculatory resistance were obtainable measurements during RHC using both temperature and pressure sensor guidewire and hyperemic agents (i.e. adenosine or papaverine) [65]. These indices detect pulmonary microvascular obstruction and can serve as a potential test of PMD.

The PA occlusion technique is a diagnostic modality, during RHC, to detect the presence of small artery and capillary-venous disease. It evaluates the pulmonary capillary pressure in small pulmonary arteries and capillaries, which allows determination of PVR upstream resistance and downstream resistance. This was validated clinically in CTEPH patients for prediction of persistent PH and survival before and after PEA [39].

5. Treatments

Pulmonary vasodilators are the medical therapy targeted toward PMD discussed in Table 4. Management of PH and subsequent RVF is focused on reducing afterload (i.e. pulmonary vasodilators in precapillary PH), optimizing preload (i.e. establishing euvolemia), and increasing RV contractility (i.e. inotropic support) [66]. Currently there is no targeted therapy focused on CMD in PH patients. Optimizing preload and reducing RV afterload may indirectly improve clearance of CMD mediators by increasing efficiency of circulating coronary blood flow.

Table 4
General approach to management of microvascular dysfunction in PH.

Group	Description	Treatments/interventions
Group 1	Pre-capillary narrowing and thickening of pulmonary artery and arterioles	• Pulmonary vasodilators • (i.e. phosphodiesterase inhibitors, endothelin receptor antagonists, prostacyclin analogs) • Maintain euvolemia • Lung transplant for refractory cases or in PVOD
Group 2	Left sided heart disease (i.e. HFpEF, HFrEF, cardiomyopathy, valvular disease)	• Maintain euvolemia • Blood pressure control (ARNI, ACE-I, aldosterone antagonists, ARB) • Address etiology of left sided heart failure with goal directed therapy
Group 3	Lung disease (i.e. COPD, ILD, OSA)	• Optimization of pulmonary disease • Inhaled Tyvaso in ILD • PPV in OSA/OHVS • Maintain euvolemia • Lung transplant
Group 4	Chronic thromboembolic pulmonary hypertension	• Pulmonary endarterectomy • Balloon pulmonary angioplasty • Riociguat • Anticoagulation • Maintain euvolemia
Group 5	Systemic disorders (i.e. sarcoidosis) Hematological disorders (i.e. sickle cell disease) Metabolic disorders Miscellaneous disorders	• Variable response to pulmonary vasodilators • Maintain euvolemia • Address underlying etiology

Legend: ACE-I, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease; OHVS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; PPV, positive pressure ventilation; PVOD, pulmonary veno-occlusive disease.

5.1. *Treatments targeting coronary microvascular dysfunction*

CMD includes coronary vasospasm and microvascular dysfunction potentially leading to myocardial ischemia [67]. Current treatments for CMD include statin therapy, calcium channel blockers, and ace inhibitors [5].

Calcium channel blockers (CCBs) are useful in the setting of prinzmetal angina and have been thought to improve coronary flow. Improving in coronary flow may result in increased coronary reserve volume and subsequently improved oxygenation and decreased CMD. CCBs were the first treatment of PAH and have largely fallen out of favor due to limited percentage of responders to vasodilator testing and development of other pulmonary vasodilators [68]. CCB use in non-responders is associated with a dose dependent risk of hemodynamic compromise [69,70].

Statins have been thought to improve CMD via anti-inflammatory and anti-atherosclerotic effects [71]. Additionally it has been noted that statins reduce the number of ischemic events in patients with documented coronary atherosclerotic disease (CAD) [72]. Furthermore, statins have been shown to reduce inflammatory markers, such as c-reactive protein, having a positive impact on reduction of inflammation yielding improvement in CAD prognosis [73]. A prior study showed that statin therapy in patients with PH secondary to lung disease is associated with increased six minute walk distance and decreased pulmonary arterial systolic pressure [74]. Statin therapy should be used in PH patients with underlying CAD and hyperlipidemia as indicated.

Angiotensin II plays a role in lung vasculature remodeling in PH patients and in myocardial remodeling [75]. Angiotensin II has been directly implicated in promoting growth of smooth muscle cells in culture models [76]. ACE inhibitor therapy is already established as an important treatment standard for systolic heart failure, implicating its benefit within Group 2 PH, but more studies are needed to determine its application to other PH groups [76,77].

5.2. *Treatments targeting pulmonary microvascular dysfunction*

There are five groups of pulmonary vasodilators used for medical therapy in PAH patients. The primary mechanism of pulmonary vasodilators is RV afterload reduction which leads to lower myocardial oxygen demand and consumption. Afterload reduction lowers RV wall stress and overdistension of the cardiac myofibrils, and allows increased coronary blood supply to the RV. Through the above mechanism, the use of pulmonary vasodilators improves microvascular function [78].

Only prostacyclin analogs have been shown to benefit mortality [79]. However other medical therapy groups have been shown to aid in improvement in quality of life, symptomatic management, and functional status of PAH patients [80]. Standard medical therapies for PAH include PDE-5 inhibitors (i.e. sildenafil and tadalafil), sGC stimulators (i.e. riociguat), prostacyclin analogs (i.e. epoprostenol, treprostinil, iloprost), prostacyclin receptor agonists (i.e. selexipag), and endothelin receptor antagonists (i.e. ambrisentan, macitentan, bosentan) [66].

Sotatercept is an emerging therapy which showed a primary end point of reduction in PVR when studied in comparison to placebo [81]. Sotatercept acts to balance both growth promoting and growth inhibiting pathways [81]. It functions as a ligand binder to block ActrIIA-Smad2/3 signaling resulting in an overall reduction of pulmonary vascular remodeling [82].

5.3. *Additional medical therapeutic considerations*

Prior cross-sectional studies have shown that vitamin D deficiency places patients at increased risk of CMD resulting in hypertension, heart failure, and ischemic heart disease [83]. One study showed a significant improvement in RV size and six minute walk test results for patients with PAH who underwent vitamin D replacement therapy [84]. Overall, vitamin D deficiency has been shown to be associated with poor prognosis in PAH patients and should be screened for routinely.

Iron deficiency is common in heart failure patients [85,86]. Additionally, iron deficiency anemia has been linked directly to the clinical course of PAH [87]. It should be screened for and addressed in heart failure patients, as it results in abnormal myocardial metabolism in the setting of impaired O2 delivery. In PAH, hypoxic inducible factors (HIFs) are part of the pulmonary vascular remodeling cascade and play a role in hypoxic vasoconstriction of the pulmonary vascular beds [88]. Iron acts as a required factor for the proteins that prompt breakdown of HIFs. In the setting of iron deficiency, HIFs can ultimately go unchecked resulting in worsening of pulmonary vascular bed remodeling and vasoconstriction [88]. Targeting iron deficiency offers an area of treatment for PH patients [87].

6. Conclusion

Microvascular dysfunction is a known process in the development of PH, yet significant investigation is needed to advance this understanding (Fig. 2). CMD is an important contributor to RVF as PH progresses and yet it is not well described in the literature. While the relationship between CMD and PMD is poorly understood, we hypothesize that there is an important interplay between the two in the development of RV-PA uncoupling. The pathogenesis of both CMD and PMD amongst the different subtypes of PH needs further investigation. Additionally, the development of invasive and noninvasive modalities to diagnose CMD of the RV are needed to elucidate its pathogenesis and contribution to RVF in PH. Pharmacological treatment options for CMD are scarce in comparison to PMD highlighting the need to better characterize CMD in PH patients.

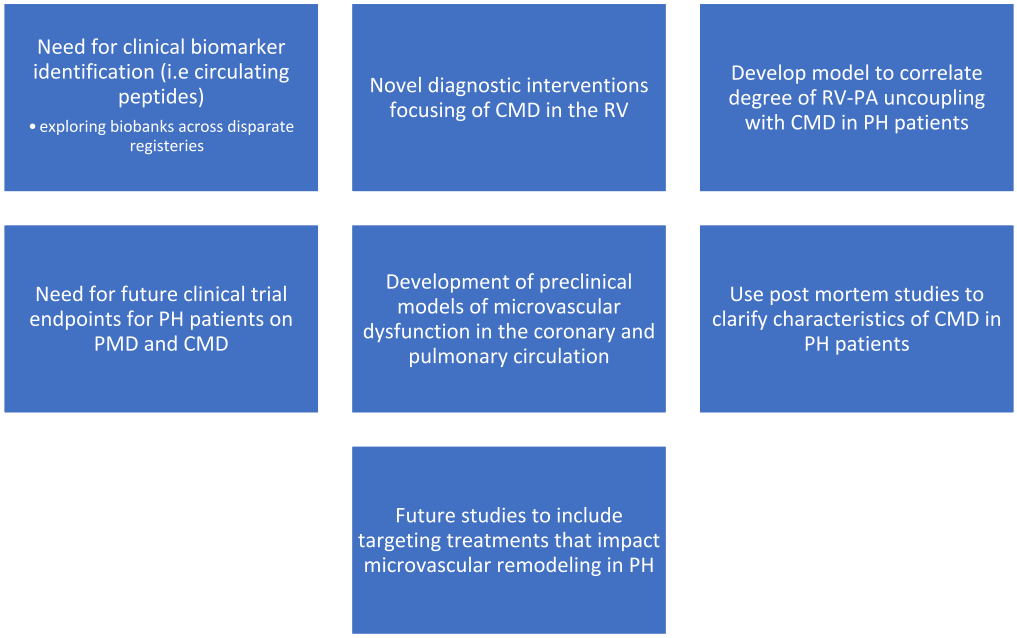

Fig. 2. Knowledge gaps in microvascular dysfunction and pulmonary hypertension.
Legend: CMD, coronary microvascular dysfunction; PH, pulmonary hypertension; PA, pulmonary artery; PMD, pulmonary microvascular dysfunction; RV, right ventricle.

CRediT authorship contribution statement

Cyrus Vahdatpour: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Supervision, Project administration. **Samuel Epstein:** Writing – original draft. **Kirk Jones:** Writing – original draft. **Madeline Smoot:** Writing – original draft. **Alex Parker:** Writing – review & editing, Supervision. **John Ryan:** Writing – review & editing, Supervision. **Andrew Bryant:** Conceptualization, Methodology, Investigation, Writing – review & editing, Supervision, Project administration.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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