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Pulmonary Hypertension in Renal Disease: Epidemiology, Potential Mechanisms and Implications

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Key Words
Pulmonary hypertension · Chronic kidney disease · End-stage renal disease · Uraemic vasculopathy

Abstract
Pulmonary hypertension (PH) is highly prevalent in end-stage renal disease. Several observational studies, based on an echocardiographic diagnosis of PH, have suggested a prevalence of 30–60% and an association with increased mortality and poorer outcome following renal transplantation. The pathogenesis of PH in this population remains poorly understood. Reported associations include arteriovenous fistulae, cardiac dysfunction, fluid overload, bone mineral disorder and non-biocompatible dialysis membranes. However, due to the small numbers, the cross-sectional nature of the majority of studies in this field, and the reliance on echocardiography for the diagnosis of PH, no consistent association with any individual risk factor has been demonstrated. There is no difference in prevalence between patients receiving different dialysis modalities and emerging evidence suggests that the onset of the condition may precede dialysis treatment in many patients. Furthermore, little is known about the impact of the 'uraemic vasculopathy' on the pulmonary vasculature. Given the similarities between vascular changes in uraemia and those seen in pulmonary arterial hypertension, it is possible that a pulmonary vasculopathy may be present in a proportion of patients. There is a need for better understanding of the natural history and the pathogenesis of the condition which would help to individualise treatment of PH in end-stage renal disease. To enable such understanding, prospective adequately powered studies with an integrated investigational approach including right heart catheterisation are needed.

Introduction

Pulmonary hypertension (PH) is defined as mean pulmonary artery pressure (mPAP) of at least 25 mm Hg at rest. The consensus Dana Point classification categorises PH into 5 distinct groups based on the aetiology or pathophysiology (table 1) [1]. A distinction is made between pulmonary arterial hypertension (PAH) (group 1) and other causes of raised pulmonary arterial pressure such as heart failure. PAH is a progressive condition characterised by endothelial dysfunction and remodelling of pulmonary vascular medial and intimal

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Table 1. Dana Point classification of PH

Group	Description	Examples
1	Pulmonary arterial hypertension	Idiopathic Hereditary Bone morphogenetic protein receptor 2 Activin receptor-like kinase 1, endoglin Unknown Drug and toxin-induced Associated with Connective tissue diseases HIV infection Portal hypertension Congenital heart diseases Schistosomiasis Chronic haemolytic anaemia
2	PH owing to left heart disease	Systolic dysfunction, diastolic dysfunction, valvular disease
3	PH owing to lung diseases and/or hypoxia	Chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing
4	Chronic thromboembolic pulmonary hypertension	
5	PH with unclear multifactorial mechanisms	Haematological disorders, e.g. myeloproliferative disorders; systemic disorders, e.g. sarcoidosis; metabolic disorders, e.g. glycogen storage disease; chronic renal failure on dialysis

layers resulting in constrictive and occlusive vascular lesions respectively. To fulfil the diagnostic criteria for PAH, the pulmonary capillary wedge pressure (PCWP) should be <15 mm Hg with pulmonary vascular resistance >3 WU.

Recent observational studies have reported a high prevalence of PH in end-stage renal disease (ESRD), particularly among haemodialysis (HD) patients [2–4] and an association with adverse outcomes.

On the Dana Point classification, PH in chronic renal failure is listed under 'group 5: PH with unclear multifactorial mechanisms'. Several studies have examined associations with potential causative factors such as arteriovenous fistulae (AVF) and bone mineral parameters [5, 6]. There has been no strong association with any individual risk factor, though the majority of these studies have shown some association with echocardiographic measures of cardiac dysfunction.

For this review we searched the literature for studies investigating PH in chronic kidney disease (CKD) and ESRD. We summarise the current state of knowledge and its limitations; in particular, we consider whether PH in CKD is a vasculopathic process akin to PAH or is merely a manifestation of cardiac dysfunction, highlighting areas requiring further research.

Epidemiology

Prevalence estimates of PH in patients with CKD are based primarily on echocardiographic parameters with little validation using the recommended gold standard right heart catheterisation (RHC). Due to the lack of prospective case-controlled studies, the timing of PH onset and its cumulative incidence at progressive stages of CKD are unknown.

Data on PH prevalence among CKD stage 5 patients prior to the initiation of renal replacement therapy (RRT) are scarce. One retrospective cohort study by Yigla et al. [7] reported a prevalence of 13.7% among 127 pre-dialysis patients, but did not provide data regarding excretory function at the time of echocardiography. Another study reported a much higher prevalence of PH in patients with advanced CKD not on RRT (39%), rising to 56% in those established on dialysis [8]. A similar prevalence in conservatively managed ESRD patients (32%) was reported by Abdelwhab and Elshinnawy [9].

In patients established on RRT, PH has been reported to be more prevalent affecting 30–58% of patients receiving HD [2, 4, 10, 11] with the largest and most recent study reporting a prevalence of 38% [12]. In patients receiving peritoneal dialysis (PD) the reported prevalence

Table 2. Summary of studies

Reference (first author)	Design	Population	Number	Definition of PH	Prevalence rate	Incidence rate
Amin 2003 [6]	cross-sectional	HD	51	sPAP >35 mm Hg	29.4%	N/A
Yigla 2003 [4]	cross-sectional	HD	58	sPAP >35 mm Hg	39.7%	N/A
Yigla 2004 [28]	cross-sectional	HD	49	sPAP >35 mm Hg	57%	N/A
Nakhoul 2005 [26]	cross-sectional	HD	42	sPAP >35 mm Hg	48%	N/A
Havlucu 2007 [8]	prospective	HD and pre-dialysis	HD: 25 pre-dialysis: 23	sPAP >35 mm Hg	HD: 56% conservative: 39%	not reported
Kumbar 2007 [13]	retrospective	PD	36	sPAP >35 mm Hg	42%	N/A
Yigla 2008 [22]	prospective	pre-dialysis prior to creation of AVF	12	sPAP >35 mm Hg	0%	41.7% after formation of AVF
Unal 2009 [3]	cross-sectional	PD	135	sPAP >35 mm Hg	12.5%	N/A
Unal 2010 [11]	prospective	HD	20	sPAP >35 mm Hg	30%	20% over a mean 23.5 months
Yigla 2009 [7]	retrospective	HD	127	sPAP >45 mm Hg	before initiation of HD: 13.4% after initiation of HD: 29%	15.7% after initiation of HD (time scale variable)
Ramasubbu 2010 [10]	longitudinal (mortality/ morbidity study)	HD	90	tricuspid jet >2.5 m/s	47%	N/A
Fabbian 2011 [2]	cross-sectional	HD and PD	HD: 29 PD: 27	sPAP >35 mm Hg	overall: 39% PD: 18.5% HD: 58.6%	N/A
Agarwal 2012 [12]	longitudinal mortality	HD	288	sPAP >35 mm Hg	38%	N/A
Pabst 2012 [14]	cross-sectional	pre-dialysis and HD with unexplained breathlessness	62	RHC mPAP >25 mm Hg pre-capillary: PCWP <15 mm Hg post-capillary: PCWP >15 mm Hg	pre-dialysis: pre-capillary: 6% post-capillary: 71% HD: pre-capillary: 13% post-capillary: 65%	N/A

varies between 12.5 and 42% [13]. Table 2 summarises these studies.

The first right heart catheter-based study of PH prevalence in CKD/HD was recently published by Pabst et al. [14] sub-classifying PH into pre- and post-capillary categories. This study compared the prevalence between a dialysis population and a pre-dialysis CKD4/5 population. In the dialysis group the prevalence was 72% which dropped to 60% when the measurements were repeated post-dialysis. In the pre-dialysis CKD group, the prevalence was 77%, with no significant difference in prevalence between the dialysis and the pre-dialysis populations. However, since unexplained dyspnoea was an inclusion criterion for this study, it does not provide a meaningful estimate of the true PH prevalence in dialysis and pre-dialysis populations.

No studies have reported a gender-specific risk for PH in renal disease. Similarly, studies that specifically looked at the prevalence of ischaemic a heart disease [7, 12, 13, 15] or traditional cardiac risk factors such as cholesterol or smoking [2, 3, 6, 13] reported no increased preponderance of these factors in patients with PH.

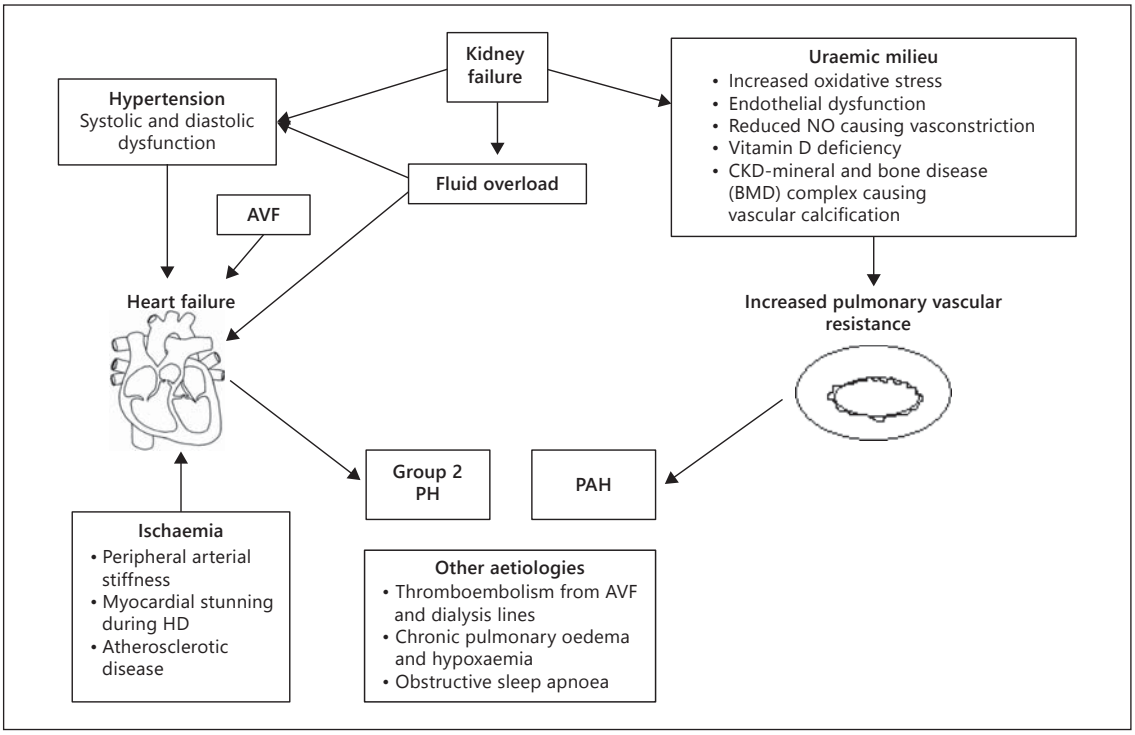

Fig. 1. Potential mechanisms contributing to PH in CKD. Hypertension, fluid overload, AVF and myocardial ischaemia result in heart failure and group 2 PH, whilst uraemic vasculopathy (vascular calcification and endothelial dysfunction) may result in increased pulmonary vascular resistance and PAH-type pathology. Other contributing factors include thromboembolism from dialysis access, chronic pulmonary oedema and obstructive sleep apnoea.

Prognostic Significance

Two prospective studies have reported an association of PH with mortality among ESRD patients. In one study of 90 patients receiving HD treatment, the 1-year survival of patients with PH was 74%, compared to 94% in patients without PH [10]. However, these figures are not adjusted for co-morbidities known to impact on survival in dialysis patients. In a more recent study of 288 patients receiving HD treatment, PH was the strongest predictor of mortality with a hazard ratio of 2.17 in a multivariate model adjusting for age, race, HD access, serum albumin and history of cardiovascular disease. Age was the only other significant predictor of mortality in the model [12]. A retrospective study by Yigla et al. [7] also demonstrated an adverse outcome in HD patients with PH after adjusting for age and the presence of valvular heart disease. This was irrespective of whether the onset of PH was before or after the initiation of HD. In patients who receive a kidney transplant, there is some evidence that those with pre-existing PH have a lower survival [16] and higher risk of early allograft dysfunction [15].

Pathophysiologic Mechanisms Explored So Far

Several mechanisms for PH in advanced CKD have been proposed and are discussed below (fig. 1).

Cardiac Dysfunction and Fluid Overload

Both systolic and diastolic cardiac dysfunctions are common in CKD. There are numerous causes for heart failure in CKD, including hypertension, salt and water overload, pleotropic effects of uraemic toxins and myocardial ischaemia. Most studies found correlations between the presence of PH and echocardiographic features of primary cardiac dysfunction. There is no consensus, however, regarding the echocardiographic findings that best predict PH in patients with advanced CKD or ESRD. In one study of 127 patients, of whom 37 had PH defined as an echocardiographically estimated systolic pulmonary artery pressure (sPAP) >45 mm Hg, there was a significantly higher prevalence of valvular disease (54% compared to 13% in those without PH), mostly mild mitral regurgitation [7]. There was a significantly higher

prevalence of left ventricular (LV) dilatation and systolic dysfunction, although there was no difference in the prevalence of LV diastolic dysfunction between patients with and without PH.

A smaller study including 56 patients on HD and PD reported that 100% of those with PH had mitral valve incompetence [2], compared to 79% of those without PH. Mitral valve incompetence in HD patients is usually functional and merely reflects the fluid status of the patient, with changes in severity according to timing of echocardiography in relation to dialysis and ultrafiltration [17]. The only other significant echocardiographic difference was ejection fraction which was significantly lower in the PH group (54 vs. 60%). In the same study, a lower diastolic blood pressure was noted in patients with PH despite a similar systolic blood pressure. This may suggest a role for arterial stiffness in the pathogenesis of the condition, as low diastolic systemic blood pressure, especially in the context of wide pulse pressure in the elderly, has been associated with increased arterial stiffness and mortality [18].

In a study of patients receiving PD, LV mass index, alongside low serum albumin and fluid overload, was a predictor of sPAP in a multivariate model [3]. Conversely, another study of patients receiving PD found no difference in the prevalence of LV hypertrophy, though LV dilatation was more prevalent in patients with PH [13].

Agarwal's study [12] also showed no difference in LV mass index between patients with PH and those without. In fact, paradoxically, patients with PH had a higher cardiac index and mid-wall fractional shortening implying a better systolic function. In a multivariate model, left atrial diameter was the strongest predictor of PH. As left atrial diameter is a strong predictor of diastolic dysfunction, the findings suggest that in this group of patients, diastolic dysfunction may be a more relevant mechanism for PH.

The diastolic dysfunction in advanced CKD patients is likely to be exacerbated by chronic fluid overload. To date, most studies of PH in CKD have failed to adequately adjust for fluid status. There are several reasons for this including the lack of a satisfactory definition of euvolaemia, the absence of a goldstandard method for assessing fluid status in the CKD population and the variation between patients in the ratio of total body water to intravascular volume.

The study of Unal et al. [3] tried to address the relationship between fluid overload and PH. Fluid overload was determined using bioimpedance studies and was expressed as extracellular to intracellular water ratio (ECW:ICW). There was a significantly higher prevalence of PH in fluid overloaded compared to normovolaemic patients (27 vs. 3.6%) with a direct correlation between ECW:ICW ratio and PAP. However, whether optimising fluid status reduced PAP was not determined.

Pabst et al. [14] showed a significant reduction in PAP, and hence prevalence of PH, when RHC and echocardiographic measurements were repeated post-dialysis. Such acute changes in PAP are most likely to be due to fluid ultrafiltration. The resultant drop in PCWP changed the diagnosis from post-capillary PH to pre-capillary PH (PAH) in 4 out of 24 patients. However, these findings should not be over-interpreted. Firstly, for the majority of the dialysis population, 'euvolaemia' achieved immediately post-dialysis is only short-lived as fluid starts to accumulate. Secondly, PCWP may be a poor indicator of LV end-diastolic pressure (LVEDP), where in one study about half of the patients diagnosed with PAH based on PCWP <15 mm Hg had elevated LVEDP on left heart catheterisation [19].

Of course, fluid overload may cause a direct lung injury from chronic pulmonary congestion adding yet a further pathophysiological mechanism to PH in these patients.

Arteriovenous Fistulae

AVF are considered the gold standard for HD access [20]. They result in increased venous return with a concomitant increase in cardiac output. Cases of 'high output cardiac failure' as a result of high AVF flow are not uncommon and often necessitate fistula ligation or reduction [21]. This was one of the first mechanisms proposed as a cause for PH in patients receiving HD. Critics of this hypothesis argue that that increased venous return alone would be incapable of increasing pulmonary artery pressure due to the compliant nature of the normal pulmonary vascular circulation, suggesting that either the pulmonary vasculature is non-compliant in these patients or other pathophysiologic mechanisms are involved. In a small prospective study following up 12 patients after the formation of an AVF, Yigla et al. [22] showed that the only significant difference between patients who developed PH (5 patients out of 12) and those who did not was higher cardiac output, suggesting that in the setting of abnormal cardiac function, an increase in flow may result in an increase in mPAP.

Two studies found no correlation between AVF flow and PH. Acarturk et al. [5] showed no significant difference in AVF flow between patients with PH and

those without in a cross-sectional study. This was confirmed in a prospective study of 20 patients by Unal et al. [11] which demonstrated no correlation between PAP and AVF blood flow. In contrast to the study of Yigla et al. [22], they demonstrated no significant increase in the incidence of PH after the formation of AVF. Another study showed a considerable reduction in the prevalence of PH post-transplantation despite standard practice of leaving AVF in situ post-transplantation [23].

In summary, the current literature suggests that formation of AVF is not a primary determinant of the development of PH in CKD.

Uraemic Toxins, Inflammation and Endothelial Dysfunction

A substantial body of evidence associates uraemia with chronic inflammation. Increases in pro-inflammatory monocytes, mast-cell proliferation, T-lymphocyte dysfunction, and decreased T-regulatory cells which result in an immune dysfunction are reported [24]. An increase in circulating inflammatory mediators also causes an increase in oxidative stress resulting in endothelial dysfunction. Patients with CKD have elevated levels of vasoconstrictors such as endothelin-1 and angiotensin II and reduced levels of endogenously produced vasodilators such as nitric oxide (NO) [25]. This imbalance of vasoactive peptides can directly affect pulmonary vascular tone and might mediate an increase in pulmonary vascular resistance causing PAH.

One study showed reduced NO levels and attenuated release of NO in response to HD in patients with PH compared to patients receiving HD without PH [26]. However, another study of 135 patients treated with PD showed no correlation between PH and asymmetric dimethylarginine, a uraemic toxin and inhibitor of NO synthase [3].

The direct effects of uraemic toxins are difficult to assess. Similarly, the effect of uraemic toxin clearance by dialysis on mortality is not fully understood. For example, the landmark HEMO study showed no overall survival benefit in patients receiving higher dose dialysis [27]. In Agarwal's study [12], a higher urea reduction ratio had a statistically significant protective effect from PH in a multivariate model. This may suggest a primary role for uraemic toxins in the pathogenesis of PH.

Bone Mineral Disorder

A major component of vascular dysfunction in kidney disease is due to vascular calcification. Therefore, calcification of the pulmonary vasculature has been proposed as a mechanism contributing to PH in CKD. One study correlated calcification score on scintigraphy scans with PH [28] and showed no association between the two. A number of studies have compared calcium, phosphate and parathyroid hormone (PTH) levels in patients with and without PH, but the majority have failed to demonstrate an association [2, 6, 22]. Only one study showed a positive correlation between echocardiographically estimated sPAP and calcium, phosphate and PTH in PD patients [13]. Failure to show a consistent relationship between bone parameters and PAP may be due to the complexity of the relationship between those parameters and cardiovascular morbidity and mortality. For example, the association between phosphate and mortality is a J- or U-shaped relationship, presumably reflecting a high degree of inflammation and malnutrition in the low phosphate group and vascular dysfunction and calcification in the high phosphate group [29, 30]. Another factor adding to the difficulty in clarifying the relationship between bone parameters and PH is the fact that imaging techniques such as scintigraphy only detect large/medium vessel calcification, when small vessel pathology is more likely to be relevant if PH is caused by an arteriopathy.

The study by Agarwal [12] demonstrated that the use of vitamin D analogues has an adjusted odds ratio of 0.41 for the presence of PH. This is consistent with a body of evidence suggesting a protective effect of vitamin D against cardiovascular mortality in CKD [31]. However, interventional studies have yet to demonstrate a convincing cardiovascular benefit of active vitamin D administration in patients with kidney disease [32]. The recent EVOLVE study also failed to show a benefit of Cinacalcet treatment for hyperparathyroidism on a composite outcome of mortality and cardiovascular events in the primary analysis [33].

Haemodialysis

The increased preponderance of PH in the HD population raises the question of whether this is related to the dialysis process itself. In particular, it has been postulated that a significant inflammatory response to non-biocompatible membranes contributes to endothelial dysfunction and subsequently PH. One study compared the changes in sPAP before and after a HD session with a cellulose membrane versus a biocompatible polysulphone high-flux dialyser. The study showed a greater reduction with the biocompatible high-flux dialyser that was not related to higher volume ultrafiltration [34]. These findings warrant further studies of the long-term impact of dialysis membranes on PH.

Unexplored Potential Mechanisms

There is a need to understand the phenomenon of PH in CKD in well-designed prospective studies taking these factors into consideration, and simultaneously evaluating cardiac dysfunction and markers of uraemic vasculopathy. The latter may prove to be an important mechanism akin to the process seen in PAH.

PAH is a progressive condition characterised by ongoing endothelial dysfunction and pulmonary vascular remodelling. The condition can be idiopathic, familial associated with specific mutations, or caused by systemic conditions such as connective tissue disease or HIV [1]. The vascular changes seen involve both the intimal and the medial layers. There is smooth muscle proliferation and matrix deposition resulting in constrictive vascular lesions. In addition, intimal hyperplasia leads to occlusive changes in the pulmonary arteries and the development of plexiform lesions. Several growth factors synthesised by dysfunctional endothelial cells have been implicated in this process including platelet-derived growth factor, epidermal growth factor and vascular endothelial growth factor. Endothelial dysfunction also results in increased synthesis of vasoconstrictors such as endothelin-1 and impaired synthesis of vasodilators such as NO. [35]. An up-regulation of some bone formation markers such as bone morphogenetic protein and osteoprotegrin have been reported in patients with PH [36].

There are similarities between this process and uraemic vasculopathy. The latter is also characterised by changes in the arterial intima and media that result in increased vascular stiffness and resistance [37]. These effects are well recognised in the systemic circulation and contribute to LV hypertrophy, but could also be important in the pulmonary circulation. Since uraemic vasculopathy is not a strictly pressure-dependent process, the lower pressures of the pulmonary compared to the systemic circulation would not necessarily confer protection from uraemic pathological remodelling. Conversely, the pulmonary vascular bed has distinct characteristics such as the response to hypoxia, that are different from the systemic circulation, thus extrapolation of data between the two systems is difficult. Active vitamin D suppresses proliferation of vascular smooth muscle cells [38], so a deficiency of active vitamin D in the setting of kidney disease (reflecting suppression of renal hydroxylation and prevalent 25-hydroxyvitamin D deficiency) may favour a hyperproliferative state similar to that seen in PAH. Although vascular smooth muscle cell proliferation is not considered a major feature of systemic uraemic vasculopathy, the uraemic-hyperphosphataemic osteochondroblastic transformation of vascular smooth muscle cells leads to arterial medial calcification and increased arterial stiffness [39]. Other mediators up-regulated by the osteochondroblastic vascular smooth muscle cell transformation, e.g. osteoprotegrin [40], could contribute to changes in the pulmonary vasculature similar to those of PAH. Impaired endothelial NO synthesis [41] and elevated levels of endothelin [25] are both features of kidney disease that cause systemic vasoconstriction but are also likely to affect the pulmonary vasculature. Therefore, although a true proliferative PAH pathology may not be induced by kidney disease, arterial changes accompanying uraemia could be a factor adding to the pulmonary resistance and right ventricular workload.

A recent association between low serum leptin levels (adjusted for BMI) and mortality in PAH has been reported [42]. A similar association between low leptin level and increased mortality among HD patients was previously reported [43]. This further suggests a similar underlying endothelial dysfunction given the stipulated role of leptin in the regulation of cardiovascular processes such as NO production.

In addition to cardiac and vascular mechanisms, there may also be a role for direct lung involvement in the development of PH in the dialysis population. Thrombi form both AVF and dialysis catheters and can lead to pulmonary thrombotic events. Septic or fibrin emboli may also result from long-term dialysis catheters. In addition, there is some evidence that the process of dialysis induces a degree of myocardial ischaemia with transient regional wall motion abnormalities [44]. This may have deleterious effects on other vascular beds, including the pulmonary bed, causing lung tissue ischaemia, another known cause for PH. Sleep apnoea is also highly prevalent in the dialysis population and may contribute to the increased prevalence of PH [45].

Limitations of Current Knowledge

The classification of patients with CKD as having PH due to unclear/multifactorial causes is a reflection of our very limited understanding of the multifactorial pathophysiologic mechanisms underlying PH in these patients. The limitations of the current body of evidence relate to the reliance on echocardiography in diagnosing PH, the lack of well-designed, adequately powered prospective studies, and the lack of mechanistic and pre-clinical studies. Some of these issues are discussed below.

Limitations of Echocardiography in the Diagnosis of PH

Various echocardiographic modalities have been utilised in the estimation of sPAP including tissue doppler echocardiography (DE), measurement of the tricuspid annular plane systolic excursion, two-dimensional strain, speckle tracking, acceleration time across the pulmonary valve, the pulmonary artery regurgitant jet method and the tricuspid regurgitant jet method [46].

The tricuspid regurgitant jet has been the most commonly used method in the studies mentioned in this review. A systematic review and meta-analysis of 29 studies with a total population of 1,998 subjects looked at the correlation of pulmonary pressures obtained by echocardiography versus RHC in order to determine the diagnostic accuracy of echocardiography for PH [46]. The correlation coefficient between sPAP estimated from echocardiography versus measured by RHC was 0.70. The sensitivity and specificity for echocardiography in diagnosing PH were 83 and 72% respectively. The minimum sPAP for diagnosis of PH in these studies was ≥30 mm Hg for echo-derived measurements and sPAP ≥30 mm Hg or mPAP ≥20 mm Hg for RHC-derived measurements.

Another study assessed the diagnostic performance of DE done within 1 h of a right heart catheter and found that DE was inaccurate (> ±10 mm Hg difference in 48% of cases). The presence of a good correlation between DE and RHC does not necessarily mean that the former can be used as a substitute for the latter, and at best may serve as a screening or surveillance but not diagnostic tool [47].

In addition, echocardiography does not provide a measure of PCWP, hence estimation of pulmonary vascular resistance, the hallmark of PAH, is not possible. Furthermore, right ventricular systolic pressure (considered equivalent to sPAP) is influenced by pre-load, including volume status and LV output, and hence does not accurately reflect changes in pulmonary vascular resistance. For example, a low right ventricular systolic pressure may be a result of reduced right ventricular output [48]. Furthermore, the timing of the measurement is also important in patients receiving HD. A pre-dialysis measurement is likely to overestimate PAP due to the fluid overload, whilst an immediate post-dialysis measurement may underestimate PAP due to redistribution of fluid for several hours post-dialysis. In addition to the fluid status, the transient myocardial stunning observed during dialysis [44] would clearly affect the echocardiographic findings, if done immediately post-HD.

Study Design Issues

Some of the limitations of the current literature are inherent to the individual study design. The majority of published studies are cross-sectional and observational. Some were designed to delineate the effect of a specific parameter such as AVF on the incidence or prevalence of PH, whilst others compared clinical characteristics of patients with and without PH. The small number of subjects in these studies, the retrospective nature of data collection in many of them and the non-invasive measures used to assess for the presence of PH are major limitations allowing only limited extrapolation.

Patients with cardiac abnormalities may have been overrepresented in many studies, such as those by Kumbar et al. [13] and Yigla et al. [7] that were retrospective and relied on historic echocardiograms. As historic echocardiograms may have been performed for the investigation of suspected cardiac dysfunction, data based on these patients would inevitably over-represent cardiac abnormalities and may exaggerate the true prevalence of PH.

Therefore, to investigate the prevalence, determinants and consequences of PH in CKD, prospective studies using RHC, preferably coupled with left heart catheterisation, need to be conducted. These studies should be accompanied by soluble and functional markers of vascular health such as cytokines, NO metabolites, assays of oxidative stress, pulse wave velocity and flow-mediated dilatation. An ideal study would be longitudinal, enrolling patients with advanced CKD and assessing the effects of interventions such as dialysis and transplantation. To date, there are no studies of the pulmonary vasculature in uraemic animal models.

Impact on Clinical Practice and Therapeutic Potential

It is unclear whether PH plays a causal role in the adverse outcomes in HD patients or is simply acting as a marker of more severe cardiac dysfunction. A PH-associated reduced capacity of the right heart to maintain adequate left heart filling pressures in the face of intermittent dialytic fluid removal could contribute to the intradialytic myocardial stunning, ischaemia and myocardial fibrosis recently described [49]. Since pro-arrhythmogenic myocardial remodelling is considered a major contributor to sudden cardiac death in the HD population, such a pathway is potentially of therapeutic importance.

Data from observational studies could help identify predictors or determinants of PH and offer new potential

therapeutic targets for clinical trials. One such example is the identification of the use of vitamin D analogues by Agarwal [12] as a protective factor.

Thus far, no interventional studies have been performed in this group of patients. An understanding of the pathophysiology could help to identify therapeutic strategies. Identifying patients with a predominant vasculopathy could facilitate selection for treatment with vasodilator therapies such as phosphodiesterase inhibitors, endothelin receptor antagonists or prostanoid analogues that have been shown to improve exercise tolerance and reduce pulmonary vascular resistance in non-uraemic PAH patients [50–52]. On the other hand, those with predominant cardiac components could benefit from strategies aimed at improving cardiac function such as the use of renin-angiotensin-aldosterone system inhibitors, intense management of fluid status, or therapeutic reduction of AVF flow. It is of utmost importance that the latter group with LV pathology are differentiated from the PAH phenotype as the use PAH treatments in patients with LV failure can result in pulmonary oedema or even death.

When designing interventional trials, it is worth bearing in mind that patients with advanced CKD may have dual pathology due to the high prevalence of systolic and diastolic cardiac dysfunction in this population. The presence of the latter should not automatically exclude the co-existence of a PAH-type process, and therefore, patients should be properly assessed for evidence of PAH and enrolled in clinical trials appropriately.

Identifying patients with potential reversibility of their PH could improve the selection process for kidney transplantation. Epidemiological data suggest that there is a high mortality rate among these patients which would preclude many of them from being considered for transplantation. Since there is some evidence that PH improves post-transplantation, patients with potential for reversibility might merit treatment with vasodilators prior to consideration for kidney transplantation.

Conclusion

The mechanisms underlying development of PH in the uraemic population may be more complex than a mere manifestation of heart failure. To understand this further, prospective studies utilising RHC should be conducted to characterise patients with intrinsic increases in pulmonary vascular resistance compared to those with left heart failure and fluid overload. Identifying the predominant mechanism in a subgroup or an individual may help to develop and individualise treatments in the future. Until better understanding of the pathophysiology and effect of interventions such as the use of vasodilator treatments in this population becomes available, there is a call for a consensus involving nephrologists and PH specialists on how best to screen for, investigate and manage these patients, and a move away from simply labelling the condition as 'heart failure'.

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