PULMONARY HYPERTENSION IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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Abstract. *Pulmonary hypertension (PH), concomitant with chronic kidney disease (CKD), is a serious but insufficiently focused disease and can lead to life-threatening conditions. Pathogenesis of LH is specific in CKD, and early diagnosis and timely appropriate treatment are important. Many studies have shown that the incidence of PH in CKD reaches almost 80% and in the future, is associated with an increase in mortality. WHO classified PH in CKD as group 5, that is, a polyetiological group of unclear genesis. Medical treatment of PH in patients with CKD is not very different from other etiologies. However, it should be understood that PH per se can be multifactorial, other secondary causes must also be recognized and addressed accordingly. In this article, we will try to discuss the concept of PH in the concept of CKD and treatment options.*

Keywords: *chronic kidney disease, end-stage renal disease, pulmonary hypertension, cardiovascular diseases.*

Introduction

CKD can lead to many systemic life-threatening conditions, including cardiovascular disease. Pulmonary hypertension, defined as elevated blood pressure in the pulmonary artery, can be defined and a separate risk factor for both morbidity and mortality in patients with CKD at various stages. Despite various theories, etiological factors for the development of pulmonary hypertension have been proposed, the generally accepted hypothesis remains an increase in cardiac ejection in patients with terminal CKD (ESRD) due to arteriovenous fistulas created for hemodialysis access. It is also covered in the sources, the presence of calcification of the pulmonary artery (LA) in patients who are treated with hemodialysis [1].

PH is defined as the mean pulmonary artery pressure (MPAP) of at least 25 mm Hg at rest. The generally accepted classification divides PH into 5 different groups based on etiology or pathophysiology (Table 1) [2]. There are differences between PH (group 1) and other causes of increased pulmonary blood pressure, for example, heart failure. PH is a progressive condition characterized by endothelial dysfunction and pulmonary vascular remodeling, resulting in vasoconstricting and occlusive vascular lesions, respectively. To fulfill the diagnostic criteria for PH, the pulmonary capillary wedge pressure (PCWP) should be < 15 mm Hg with pulmonary vascular resistance > 3 WU.

Recent studies have shown a high prevalence of PH in patients with end-stage CKD (ESRD), especially among patients with hemodialysis (HD) [3-5} and their subsequent association with adverse consequences.

The World Health Organization (WHO) classified PH into five groups based on etiology, which was further revised in 2003 and 2008.

Group 1 includes (idiopathic pulmonary arterial hypertension (ILH), drug or toxin-induced pulmonary hypertension, hereditary pulmonary hypertension, collagenoses, HIV infection, parasitic infections, and chronic hemolytic anemia. In group 2 - PH caused by left ventricular heart failure, valvular heart disease, pulmonary occlusive disease, venous disease and external

compression of pulmonary veins are included. Group 3 PH includes PH resulting from chronic lung diseases, including nocturnal apnea syndrome [6]. PH group 4 - chronic thromboembolic pulmonary hypertension (CTP). Group 5 addresses PH with other, less clear or multifactorial etiologies, including ESRD. We want to pay attention to PH, secondary to the last stage of kidney disease (ESRD).

Estimates of LH prevalence in CKD patients are based on basic, echocardiographic (EchoCG) parameters and with little use of the recommended gold standard for diagnosis of LH - right heart catheterization (RHC). Due to the lack of prospective studies, the time to onset of PH and its frequency in the gradual stages of CKD are unknown.

There is very little data on the prevalence of LNG among patients with stage 5 CKD prior to initiation of renal replacement therapy (RRT). According to a study conducted by Yigla et al. [7], the prevalence of the disease among 127 patients in the pre-dialysis stage was 13.7%, but did not contain data on excretion function at the time of echocardiography. Another study reported a much higher prevalence of PH in patients with late CKD rather than TPD (39%), which increased to 56% in patients on dialysis [8].. A similar prevalence among conservatively managed ESRD patients (32%) was reported by Abdelkhov and Elshinavi [9]. It is reported that in patients with established PH, 30-58% of patients receiving HD are more common [3, 5, 11, 12]; at the same time, the largest and most recent study showed that the prevalence of PH is 38%. [10]. In patients receiving peritoneal dialysis (PD), the reported prevalence ranges from 12.5 to 42% [13]

Table 1 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 [5]	cross-sectional	HD	58	sPAP >35 mm Hg	39.7%	N/A
	cross-sectional	HD	49	sPAP >35 mm Hg	57%	N/A
Yigla 2004 [13]	cross-sectional	HD	42	sPAP >35 mm Hg	48%	N/A
	prospective	HD and	HD: 25	sPAP >35 mm Hg	HD: 56%	not reported
Nakhoul 2005 [14]		pre-dialysis	pre-dialysis: 23		conservative: 39%	
Havlucu 2007 [8]	retrospective	PD	36	sPAP >35 mm Hg	42%	N/A
	prospective	pre-dialysis prior	12	sPAP >35 mm Hg	0%	41.7% after forma-
Kumbar 2007 [13]		to creation of AVF				tion of AVF
	cross-	PD	135	sPAP >35 mm Hg	12.5%	N/A

	sectional					
Yigla 2008 [15]	prospective	HD	20	sPAP >35 mm Hg	30%	20% over a mean
						23.5 months
Unal 2009 [4]	retrospectiv e	HD	127	sPAP >45 mm Hg	before initiation of	15.7% after
					HD: 13.4% after initiation of HD: 29%	initiation of HD
Unal 2010 [11]						(time scale variable)
	longitudinal	HD	90	tricuspid jet >2.5 m/s	47%	N/A
Yigla 2009 [7]	(mortality/ morbidity study)					
	cross-sectional	HD and PD	HD: 29	sPAP >35 mm Hg	overall: 39%	N/A
Ramasubbu 2010 [11]			PD: 27		PD: 18.5%	
					HD: 58.6%	
	longitudinal	HD	288	sPAP >35 mm Hg	38%	N/A
Fabbian 2011 [3]	mortality					
	cross-sectional	pre-dialysis	62	RHC mPAP >25 mm Hg	pre-dialysis:	N/A
		and HD with unex-		pre-capillary:	pre-capillary: 6%	
Agarwal 2012 [10]		plained breathless-		PCWP <15 mm Hg	post-capillary: 71%	
		ness		post-capillary:	HD:	
Pabst 2012 [16]				PCWP >15 mm Hg	pre-capillary: 13% post-capillary: 65%	

None of the studies reported a gender difference in ROP risk in chronic kidney disease. Similarly, studies that examined the prevalence of coronary heart disease [7, 12, 13, 17] or traditional heart risk factors such as cholesterol or smoking [3, 4, 7, 13] did not reveal any definite predominance of these factors in patients with PH.

The following mechanisms for the development of PH in patients with CKD were also proposed for discussion (Fig. 1). The spread of both systolic and diastolic cardiovascular dysfunctions in patients with CKD is known. There are also many causes of heart failure in CKD, including hypertension, salt and water overload, supplemental effects of uremia, and myocardial ischemia. Most studies have found that there is a correlation between the presence of PH and echocardiographic features of primary cardiac dysfunction. At the same time, there is no consensus regarding echocardiographic findings that best predict PH in patients with far-advanced CKD or ESRD. In one study, 127 patients, 37 of whom PH was defined as echocardiographic pulmonary

artery systolic pressure (sPAP) > 45 mm Hg, had a significantly higher prevalence of valvular disease (54% versus 13% in patients without PH), mainly mitral regurgitation [7]. There was a significant prevalence of left ventricular dilatation (LV) and systolic dysfunction, however there were no correlation relationships in the prevalence of diastolic LV dysfunction in patients with and without PH.

Less extensive study including 56 patients on HD with concomitant PH reported that 100% of those with PH had mitral valve in-competence [3], compared to 79% of those without PH. Mitral valve incompetence in patients on HD 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 [18]. The only other significant echocardiographic difference was ejection fraction which was significantly lower in thePH group (54 vs. 60%). The same study noted such a phenomenon as decreased diastolic blood pressure, which was noted in patients with PH despite similar systolic blood pressure. Which may indicate a role in the pathogenesis of arterial stiffness, since low diastolic systemic blood pressure, especially in the context of a wide range of pulse pressure in the elderly, was associated with increased arterial stiffness and mortality [19]. In a study of patients on program HD, LV mass index, along with low serum albumin and fluid overload, was an sPAP marker in a multivariate model [4]. Conversely, another study of patients on program HD showed no difference in the prevalence of LV hypertrophy, although LV dilation was more common in patients with PH [13].

Agarwal's study [12] also showed no discrepancies in the LV mass index in patients with and without LH. In fact, paradoxically, patients with PH had a higher cardiac index and fractional shortening of the middle wall, implying better systolic function. In a multivariate model, the left atrial diameter was the strongest marker of PH. Because left atrial diameter is a direct marker of the presence of diastolic dysfunction, the findings suggest that in a given group of patients, diastolic dysfunction may be a more significant mechanism for PH.

There is a possibility that Diastolic dysfunction in advanced patients with CKD is likely to be exacerbated by chronic fluid overload. To date, most PH studies in CKD patients have failed to adequately assess and adapt to excess fluid. This is due to several reasons, including the lack of a satisfactory definition of evolemia, the lack of Gold standard's method for assessing the condition of fluid in the CKD population, and the variation of patients in the ratio of total body water volume to intravascular volume.

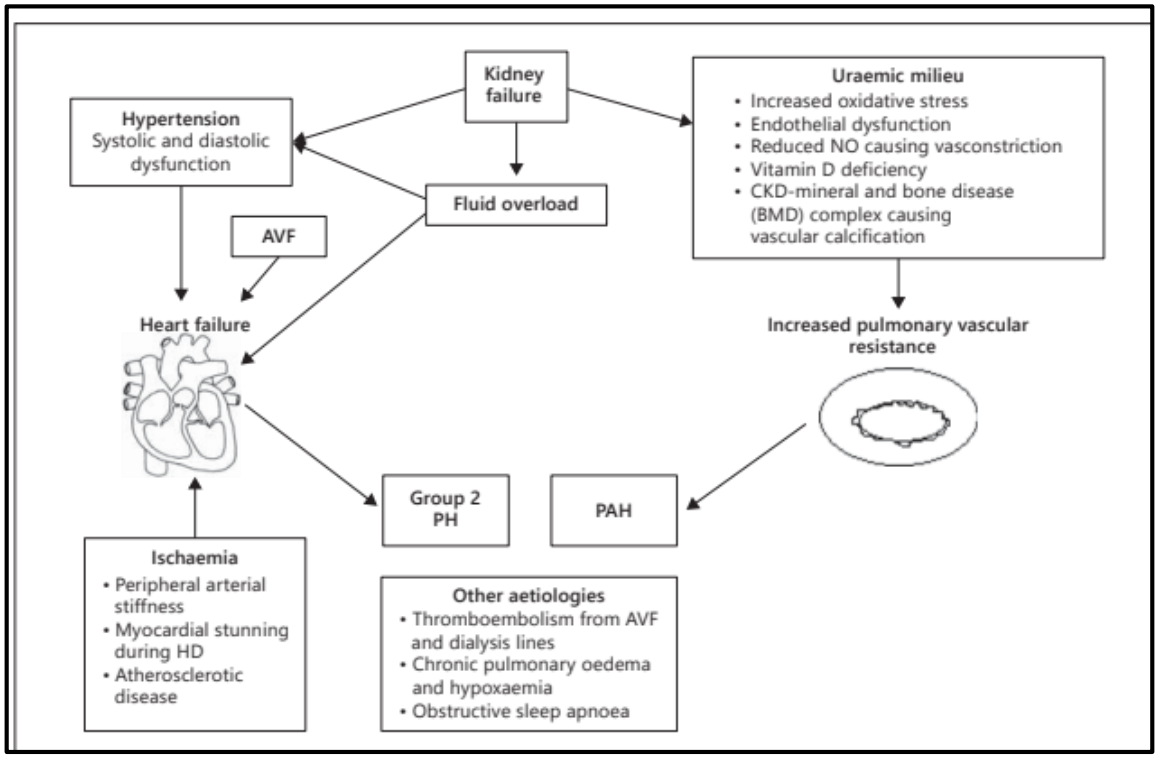
The study of Unal et al. [4] tried to address the relationship between fluid overload and PH. Fluid overload was determined using bioimpedance studies and wasexpressed as extracellular to intracellular water ratio (ECW:ICW). There was a significantly higher prevalence of PH in fluid overloaded compared to normovolaemic patients (27 vs. 3.6%) with a direct correlation between ECW:ICW ratio and PAP. However, whether optimizing fluid status reduced PAP was not determined.

Pabst et al. [16] showed a significant reduction in PAP,and hence prevalence of PH, when RHC and echocardiographic measurements were repeated post-dialysis. Suchacute 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 interpret straightforwardly. First off all , for most dialysis populations, euvolemia achieved immediately after dialysis does not last long, that is, as fluid accumulates. Secondl off all, PCWP may be a poor indicator ofLV 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 [20].

Of course, excessive fluid loading can cause direct damage due to chronic pulmonary overload by adding another pathophysiological mechanism to consider the development of PH in patients with CKD

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



Although radiological studies of the chest rarely detect calcifications, an autopsy of patients with ESRD showed that up to 40-80% of them had metastatic calcifications, [20]. Chronically elevated parat-hormone levels are a hallmark of ESRD and lead to calcium mobilization into cells. Akmal et al suggested that secondary hyperparathyroidism may be one of the main processes during calcification of the pulmonary artery [21]. It is also noted that the secondary PH is associated with functional abnormalities of the right ventricle. This was also confirmed by experimental surgical removal of the parathyroid glands in dogs with chronic renal failure, followed by a decrease in pulmonary artery calcification. In addition to pulmonary calcification, hormonal and metabolic changes in ESRD lead to vasoconstriction, also leading to the development and aggravation of pulmonary hypertension [23]. Levels of vasoactive substances, including tumor necrosis factor alpha (TNF- α), interleukin 1b (IL-1B), IL-6, acute phase proteins, etc., were high in this subgroup of patients indicating chronic inflammatory etiology [24]. In this patients also had higher levels of nitric oxide that was fractionally excreted in the airways.

In patients in ESRD, arterio-venous (AV) fistula that is surgically made in the patients who are on dialysis is the cause of pulmonary hypertension in a considerable population, though most of the patients who have pulmonary hypertension have co-existing heart conditions contributing to the elevated pulmonary arterial pressure. PH can develop quickly after fistula formation sometimes

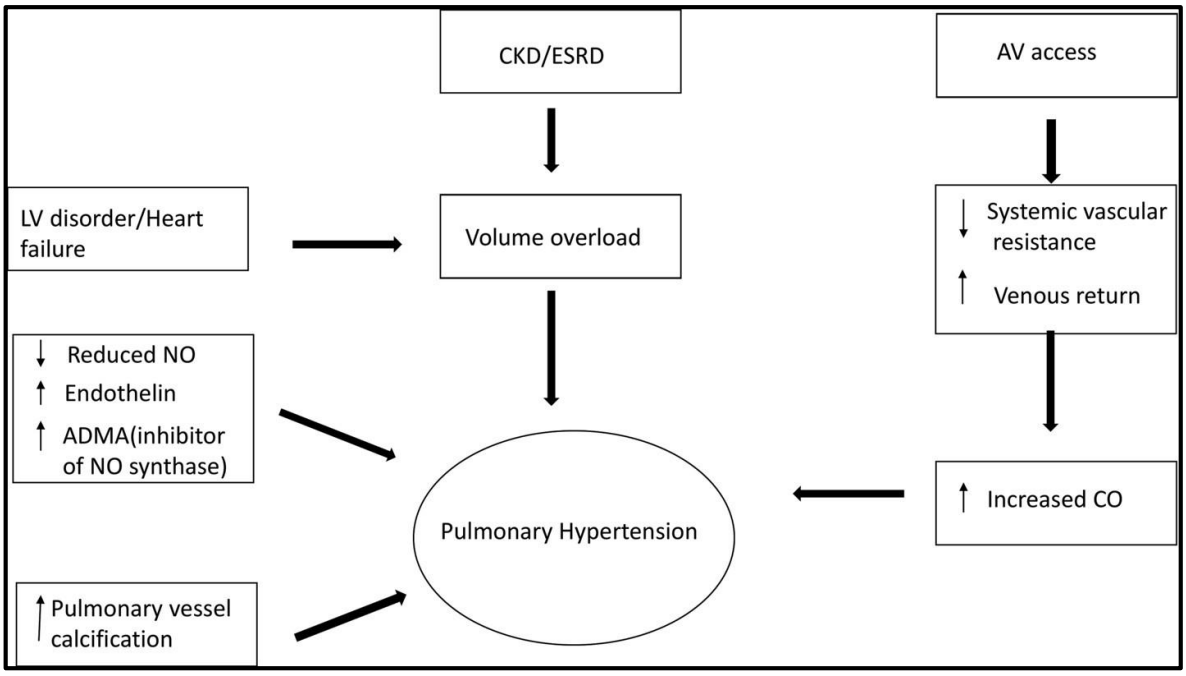
even before the commencement of hemodialysis through the fistula [25]. The significant increase in cardiac output reduced systemic vascular resistance and hence increased venous return often caused by the AV fistula needs to be accommodated by the pulmonary vessels. Endothelial dysfunction noted in these vessels due to ESRD causes decreased ability to adapt to the higher cardiac output and results in increased PA pressure [26].

This is also further supported by the reduced levels of nitric oxide in patients with PH in ESRD and the levels improve with hemodialysis. Together with reduced NO, there is also increased asymmetric dimethylarginine (ADMA) which is an inhibitor of endothelin synthase.

The possible causes of PH and the associated confounding factors in patients with ESRD with and without AV fistula are depicted in the figure (Fig. 2). Volume overload in ESRD is a direct cause of increased blood pressure in the PA from increased after-load, especially if there is co-existing LV disorder. Interestingly PH can regress if the AV fistula is closed or after renal transplant. The presence of PH in patients on GD does increase the mortality rate and kidney transplants should be considered in ESRD patients with known prior PH. The same applies if a patient develops PH after initiation of renal replacement therapy with hemodialysis. Also, no benefit was found for survival in peritoneal dialysis over

GD, although this is not due to the need to create AV fistula [27]. This proves that in addition to the AV fistula, there are other parameters associated with the pathogenesis of pulmonary hypertension in ESRD. Chronic anemia in patients with ESRD is definitely an important cause of hypoxia, which further leads to the development of PH.

Fig. 2 Possible pathogenesis of PH to CKD/ESRD patients



A significant number of studies have shown a link between uremia and chronic inflammation. There is an increase in inflammatory monocytes, proliferation of mast cells, T-lymphocyte dysfunction and a decrease in T-regulatory cells, which lead to an imbalance of the immune system [28]. An increase incirculating inflammatory mediators also causes an in- crease 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 vasodilators such as nitric oxide (NO) [29]. This disbalance of vasoactive peptides can directly affect pulmonary vascular tone andmight mediate an increase in pulmonary vascular resistance causing PAH.

One of the studies showed a decrease in the level of NO and attenuated release of NO in patients on HD in patients with PH compared to patients treated with HD without PH [30]. However, another study of 135 patients treated with HD showed no correlation relationships between PH and asymmetric dimethylarginine, uremic toxin, and NO sythase inhibitor. [4].

The direct effects of uremic toxins are difficult to assess. Similarly, the effect of uremic toxin clearance in dialysis on mortality is not fully understood. For example, the landmark HEMO study showed no overall survival benefit in patients treated with higher-dose dialysis [31]. In Agarwal's study [12], a higher urea reduction ratio had a statistically significant protective effect against PH in a multivariate model. This may indicate a major role for uremic toxins in PH pathogenesis.

It is noted above that the main component of vascular dysfunction in kidney disease is vascular calcification. Therefore, calcification of the pulmonary vasculature has been proposed as another mechanism contributing to the development and progression of PH in CKD. One study states a correlation assessment of calcification in scintigraphy scans with PH [32] and has not statistically shown an association between the two. In a number of other studies, a comparative assessment of the level of calcium, phosphate and parathyroid hormone (PTH) in patients with and without PH was carried out, but even here the majority could not demonstrate an association [3,6,15]. And only one study showed a positive correlation between echocardiographically assessed sPAP and calcium, phosphate and PTH in a PD patients [13]. Failure to show a consistent relationship be- tween bone parameters and PAP may be due to the complexity of the relationship between those parameters andcardiovascular morbidity and mortality. For example, theassociation between phosphate and mortality is a J- or U-shaped relationship, presumably reflecting a high degreeof inflammation and malnutrition in the low phosphate group and vascular dysfunction and calcification in the high phosphate group [33, 34]. Another factor adding difficulty in elucidating the relationship between mineral parameters and PH is the fact that imaging techniques such as scintigraphy only detect calcification of large/medium vessels, in turn when small vessel pathology is more likely to matter if PH is caused by arteriopathy.

Despite the fact that intervention studies have not yet demonstrated a convincing cardiovascular benefit of active vitamin D administration in patients with kidney disease [35], Agarwal's work [12] demonstrated that the use of vitamin D analogues has an adjusted odds ratio of 0.41 for the presence of PH. This intersects with a lot of evidence showing the protection of vitamin D against cardiovascular mortality in CKD [36]. The recent EVOLVE study also failed to show a benefit of Cinacalcet treatment for hyperparathyroidism on a composite out- come of mortality and cardiovascular events in the primary analysis [37].

At this time, there were no interventional studies in the group of CKD patients with PH. Understanding pathophysiology could help define therapeutic strategies. Identifying patients with predominant vasculopus may facilitate choice for treatment with vasodilator therapies such as phosphodiesterase inhibitors, endothelin receptor antagonists, or prostanoid analogs that have been shown to improve exercise tolerance and reduce pulmonary vessel resistance in patients with non-renal PAH [38-40]. On the other hand, that group of patients dominated by cardiac components may further improve cardiac functions, such as the use of renin-angiotensin-aldosterone system inhibitors, which will be able to intensively manage fluid status or therapeutic reduction of AVP flow. However, it is critical that the latter group with LV pathology differ from the PAH

phenotype, since the use of PAH treatment in patients with LV insufficiency can lead to pulmonary edema or even death.

When developing interventional research papers, it is worth remembering that patients with advanced CKD may have dual pathology due to the high prevalence of both systolic and diastolic cardiac dysfunction in this population. But the presence of the latter should not automatically rule out coexistence of the PAH-type process, and therefore patients should be properly assessed for signs of PAH and appropriately included in clinical trials.

Conclusion:

Timely identification of patients with potential reversibility of their PH may improve the selection process for kidney transplantation. Epidemiological evidence suggests that there is a high mortality rate among this group of patients, which would obviously prevent many of them from being considered for transplant transition. There is also some evidence that PH improves after transplantation, patients with reversibility potential should consider treatment with vasodilators before considering kidney transplantation.

Monitoring pulmonary pressure will be justified when symptoms worsen despite treatment. Catheterization of the right heart is a useful but inaccurate measurement of PA pressure, and in sick HD patients, contribution from AV fistula can be determined by manual compression of the same when measuring PA pressure during RHC. Echocardiogram is a non-invasive, sensitive method for diagnosing RV systolic pressure. Blood flow in the fistula measured by Doppler can be used to assess the state of the AV fistula and the need to reduce flow by ligation or bandage [23,30]. Pulmonary hypertension is an independent predictor of increased mortality in patients with end-stage renal disease. It is necessary to wound diagnosis and treatment to prevent life-threatening complications. More research in this area is needed to better understand the mechanisms of pathogenesis and treatment tactics. To date, there has been a call for consensus with nephrologists and PH specialists on when and how best to screen for PH, investigate and refer these patients, and move away from simply labeling the condition as "chronic heart failure" until a better understanding of the pathophysiology and effect of interventions, such as the use of vasodilating therapies in this population, becomes available.

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