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Pulmonary Hypertension in CKD: Some Answers, Yet More Questions

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Pulmonary hypertension (PH), defined as a mean pulmonary artery pressure (mPAP) ≥25 mmHg, is described in numerous pathologic conditions and its presence is typically associated with worse outcomes. Experts in the field have established a clinical classification system which places patients with PH into five groups according to shared pathobiology, clinical presentation, and therapeutic approaches.[1] Although patients with CKD exhibit many symptoms and risk factors associated with PH, literature describing the epidemiology and impact of PH in CKD has been limited. Until recently, in fact, this literature was limited to CKD stages 4 and 5 with and without dialysis dependency. In these patients with advanced CKD, PH is prevalent (approximately 30%–40%) and associated with worse outcomes.[2,3] Reflective of poor insight into the nature of PH in this population, individuals with PH and ESRD are included in group 5 PH – that due to cryptic or multifactorial etiologies. The larger population with earlier stages of CKD bears a very high burden of cardiovascular morbidity and mortality; therefore, gaining additional knowledge related to PH in this population is of clinical relevance.

The current study from Navaneethan *et al.* leverages the power of the Chronic Renal Insufficiency Cohort (CRIC), a large (n=2959) longitudinal cohort study of subjects with eGFR 20–70 ml/min per 1.73 m^2, providing the most comprehensive description to date of PH prevalence and significance in a nondialysis CKD population.[4] CRIC subjects underwent transthoracic Doppler echocardiography (TTE) interpreted centrally in a core laboratory, as well as detailed ascertainment of covariates and comorbid conditions, and thorough adjudication of cardiovascular and kidney outcomes. The authors used an accepted echocardiographic case definition of PH: pulmonary artery systolic pressure (ePASP) >35 mmHg and/or tricuspid regurgitant velocity >2.5 m/s.

Concordant with recent studies from Italy and China,[5,6] PH was prevalent in the CRIC, present in roughly one in five subjects (21%), and was significantly and indirectly related to the eGFR, rising from 6% among CKD stage 1 to 33% in CKD stage 5. As has been described in other studies, PH was associated with older age, systemic hypertension, diabetes, and a history of heart failure (HF).[5,7] Multivariable analysis found that older age, lower hemoglobin, lower left ventricular ejection fraction, and the presence of left ventricular hypertrophy were independently associated with PH. The presence of PH was associated with a 38% increased risk of overall mortality and a 23% increased risk of cardiovascular events (HF, myocardial infarction, cerebrovascular accident, and peripheral vascular disease). In this cohort PH was not associated with progression of CKD.

This study has value, not only for the relative novelty of the message that PH is prevalent in all stages of CKD, but additionally for its ability to assess predictors and mortality related to PH using a more systematized approach than prior studies. Despite this, however, there are several limitations which prevent the formation of insights into PH pathogenesis in CKD and, by extension, the adoption of targeted therapeutic approaches. First, the study utilizes ePASP as a proxy for invasive hemodynamic measures. While echocardiography provides a reliable estimate of ePASP,[8] its utility as a tool for

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distinguishing between groups of PH is still in evolution. Per the current World Health Organization guidelines, right heart catheterization (RHC) is still required to provide a complete hemodynamic classification of PH and subsequently inform appropriate use of PH group-specific therapy.[9] Use of ePASP in the present study thus limits our ability to understand the type, the pathogenesis, and therefore the best therapeutic approach to PH in the CKD population.

Elevations in pulmonary pressures can arise in the setting of several distinct physiologic perturbations. In the pulmonary circulation, the relationship between vascular resistance, flow, and pressure is described by Ohm's Law: mPAP = pulmonary vascular resistance (PVR) × cardiac output + pulmonary capillary wedge pressure (PCWP). Thus increases in PVR, cardiac output, and venous pressure (estimated by PCWP) all may result in PH. It should be appreciated that the present five-group clinical classification of PH is not aligned with unique group-specific hemodynamic criteria – in fact, the only specific hemodynamic criterion considered (beyond mPAP) is the PCWP, which if elevated (>15 mmHg) maps to a group 2 PH classification. Elevated PVR, while previously considered specific to group 1 pulmonary arterial hypertension (PAH), has been identified in subpopulations of all PH groups. Patients with CKD may exhibit variable hemodynamic patterns and clinical risk profiles associated with PH as indicated in Table 1.

Although this paper does not include invasive hemodynamics, one might suspect that the majority of PH in CKD may result from a hypervolemic and/or hyperdynamic mechanism due to the hypervolemia, anemia, and frequency of other cardiovascular disease in this population. This assumption was partly validated in the prevalence of precapillary PAH in patients with ESRD (PEPPER) study, in which consecutive patients with CKD stages 4 or 5 undergoing evaluation for unexplained dyspnea underwent TTE and RHC.[7] The authors report a very high prevalence of PH (approximately 70%) with a large majority (90%) having hemodynamics consistent with the hypervolemic model (elevated PCWP). Of additional interest in this study, patients receiving hemodialysis were catheterized before and after dialysis; concluding that accurate identification of group 1 PAH was only possible after removal of fluid. Despite the appeal of extrapolating PEPPER to the CRIC population, we are also mindful that while the CKD population shares many risk factors with group 2 PH such as diabetes, hypertension, and HF, there is also a high prevalence of autoimmune and lung diseases, which may predispose to group 1 PAH and group 3 PH, respectively.

A second limitation is the lack of data on right ventricular (RV) function. It is often said that patients with PH die when the RV fails and investigators have shown that symptoms and survival are highly correlated with RV dysfunction.[10,11] In the present study, the absence of data on RV function makes it very difficult, even with adjudication, to understand the potential causality between PH and mortality. Are patients with CKD and PH dying of RV failure, as has been demonstrated in other forms of PH, or is the presence and association with outcomes simply a reflection of other cardiovascular disease, such as coronary disease and left ventricular hypertrophy? There are numerous validated echocardiographic parameters of RV function and morphology that could have been considered and potentially applied in this study.[12] Understanding the relationship between the PAP and RV (PA-RV coupling) is not only critical to understanding pathogenesis, but also to defining effective therapeutic approaches.

The last limitation, which is perhaps less important, relates to the diagnosis of HF. One of the stronger outcome associations noted with PH in CRIC was with HF. HF is a challenging diagnosis in CKD due to the fact that chronic fluid retention, edema, and elevated jugular venous pressure (all part of the definition of HF in CRIC) may either be due to HF (right- or left-sided) or fluid retention secondary to proteinuria or reduced GFR. The implications and treatments based on the etiology and the type of HF may be different.

Two interesting subgroup results deserve attention. First, the association of PH with outcomes was notably stronger in women than men (Supplemental Figures 4 and 5 in Navaneethan *et al.*[4]). This is in contrast to studies in both group 1 PAH and group 2 PH that found the opposite: that men with PH fare worse than women, perhaps due to sex hormone–mediated differences in RV structure and adaptation.[10,13,14] Second, PH was more prevalent in non-Hispanic blacks than other racial or ethnic groups. Blacks are known to have more severe and longer duration of hypertension than whites, which may lead to worse left-sided heart disease and an increased risk of PH. Cosegregating risks, and differential genetic or socioeconomic influences may also be important. Closer examination of such sex and racial/ethnic differences may offer novel insights into pathogenesis and therapeutic options.

Despite the limitations mentioned above, the present study provides some of the most compelling data associating PH with CKD and mortality. What are the implications from the research standpoint? First, these results need to be verified in additional and diverse populations. Second, future studies should incorporate RV assessments and RHC and ideally they should include patients with mild, moderate, and severe PH. Third, given the relationship between PH

Table 1. Hemodynamic patterns of pulmonary hypertension

	Hyperdynamic[b]	Hypervolemic	High Resistance[a]
PAP	↑	↑	↑
PCWP	normal/↑	↑	normal
CO	↑	normal	normal
PVR[a]	normal	normal	↑
Applicability to CKD	AVF, anemia	Volume overload	Autoimmune disease

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; CO, cardiac output; PVR, pulmonary vascular resistance; AVF, arteriovenous fistula.

[a]The pulmonary arterial bed of some of individuals with longstanding hyperdynamic or hypervolemic circulation will remodel, leading to increases in PVR and a hemodynamic profile that exhibits a high resistance pattern that is similar to that seen in group 1 PAH.

[b]High output cardiac failure with associated PH is reported in several clinical entities; most of these are currently classified as group 5.

and exposure to high volume and high flow states, studies should examine the natural history of PH throughout the progression of CKD. Correlation between PH, its reversibility, and BP and volume status over time would provide insight into the mechanisms that drive pulmonary vascular remodeling (equating to increased pulmonary vascular resistance) in this population. Finally, studies should incorporate detailed assessments of lung disease and sleep apnea, as these comorbidities are prevalent in CKD, and are associated independently with PH.

What are the implications from the clinical standpoint? First and foremost, clinicians must recognize that PH is common and morbid in CKD. Second, TTE is a safe and valid screening test for PH. Third, RHC should be strongly considered in symptomatic patients with ePASP >35 mmHg and/or right atrial or RV dilatation. The importance of proper phenotyping *via* RHC should not be underestimated. Although there are several agents used for treatment of group 1 PAH, their use in other types of PH has not shown benefit, and in some cases can cause harm. Accurate hemodynamic assessments will distinguish between those CKD patients who might benefit from group 1 PAH–specific therapy, and those in whom more aggressive management of risk factors such as volume and hyperdynamic status is more appropriate.

In summary, PH is highly prevalent in CKD and associated with adverse outcomes. Although we do not yet understand the pathophysiologic range of PH in the CKD population, its presence is clearly important to the individual patient. However, additional studies are needed so as to translate these data into improved care for patients.

DISCLOSURES

None.

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Apheresis to Treat Preeclampsia: Insights, Opportunities and Challenges

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Preeclampsia, a hypertensive condition unique to pregnancy, remains a significant source of maternal and neonatal morbidity

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