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Pulmonary hypertension in chronic kidney disease: a hemodynamic characterization

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Pulmonary hypertension (PH) is a common co-morbidity in patients with chronic kidney disease (CKD) and end-stage renal disease.[1–3] More importantly, the presence of PH is associated with increased risk of hospitalization and mortality in patients with CKD.[3,4]

Despite its prognostic significance, the true prevalence of PH in CKD is unclear. The majority of prior studies reporting the prevalence of PH in patients with CKD have defined PH based on echocardiography,[1–3] which is frequently inaccurate.[5]

In addition, the pathogenesis of PH in CKD are not well defined. Many different mechanisms may play a role.[6] In light of this, the current World Health Organization (WHO) categorizes PH due to CKD and end-stage renal disease under WHO group 5, "miscellaneous causes". Patients with CKD often have coexisting left heart disease, chronic lung disease, thromboembolic disease, autoimmune diseases including scleroderma and systemic lupus erythematosus, and liver disease, that are well-established risk factors for developing PH. Additionally, CKD, especially end-stage renal disease, by itself has also been proposed to cause pulmonary vascular remodeling and PH. Possible mechanisms that have been suggested include endothelial dysfunction due to increased oxidative stress from uremic toxins, chronic inflammation resulting from exposure of the blood to dialysis membrane, vascular calcification, and increased flow from arteriovenous fistula (reviewed in Kawar et al.[6]). However, these mechanisms are not supported by robust preclinical or clinical studies.

In this issue of *Pulmonary Circulation*, O'Leary et al. sought to address these knowledge gaps by studying the prevalence, associated risk factors, and prognostic importance of PH in a large, electronic record-based cohort of patients who were referred to the Vanderbilt University cardiac catheterization lab for a right heart catheterization (RHC). Renal function was determined by estimated glomerular filtration rate using the CKD-EPI creatinine equation. Only patients with stage 3 or worse CKD were included and those with stage 2 or less kidney disease were excluded. Clinical, laboratory, and hemodynamic data were extracted from the electronic health records. Co-morbidities were defined by International Classification of Diseases (ICD)-9 codes. Notably, patients with complex congenital heart disease, chronic thromboembolic disease, acute myocardial infarction, and previous lung or cardiac transplantation were excluded. Vital statistics were obtained using Social Security death index.

PH, defined as mean pulmonary artery pressure (mPAP) $\geq$ 25 mmHg, was present in 68% of patients in this cohort. Post-capillary PH, defined as mPAP $\geq$ 25 mmHg with a pulmonary capillary wedge pressure (PCWP) > 15 mmHg, was more common than pre-capillary PH, defined as mPAP $\geq$ 25 mmHg with a PCWP $\leq$ 15 mmHg (76% vs. 24%, respectively). PH was more likely to be present in CKD patients who were younger, African Americans, and those who had diabetes, obesity, scleroderma, left heart disease, obstructive sleep apnea, and chronic obstructive pulmonary disease. Although many of the patients with pre-capillary PH had established risk factors for pulmonary vascular disease such as scleroderma, systemic lupus erythematosus, cirrhosis, human immunodeficiency virus infection, and chronic hypoxic lung disease, 58% of them had no known risk factors. The presence of CKD was associated with 1.4-fold increased risk of having PH after adjusting for other independent risk factors for PH in this cohort. Finally, consistent with prior reports, the presence of PH was associated with increased risk of mortality in patients with stage 3 or worse CKD.

O'Leary et al. should be congratulated for this informative study. To the best of our knowledge, this is the largest study to use invasive hemodynamics to diagnosis and characterize PH in patients with CKD as opposed to using Doppler estimated pulmonary artery pressures. This is crucial, as the echocardiogram cannot only under- or over-estimate PAPs, but it is also limited in differentiating whether the elevated PAPs are due to pre-capillary pulmonary vascular remodeling, increased left sided filling pressure, or high cardiac output. All these mechanisms may cause PH in patients with CKD.

Several aspects of this study are noteworthy. First, the prevalence of PH in CKD reported in this study is

considerably higher in comparison to prior studies (68% vs. 30–40%).[1,2] This is probably an overestimation due to referral bias. The authors studied only CKD patients who were referred for a cardiac catheterization in a tertiary care referral center as opposed to all patients with CKD. Patients who undergo a clinically indicated RHCs are more likely to have abnormal PAPs. Thus, this prevalence data may not be applicable to all patients with CKD.

Second, in this study, nearly half of the patients with pre-capillary PH had no identifiable risk factors for pulmonary vascular remodeling, and the majority of them were female. Based on this, the authors propose a direct, sex-specific, pathophysiological relationship between PH and CKD, i.e. CKD itself may causes pulmonary vascular disease. Although these observations are intriguing, there are several elements that merit consideration. In this study, the risk factors for PH were identified using ICD codes in electronic health records. This approach is not precise when compared to prospective registries. Thus, it is conceivable that some risk factor for PH were not captured. Additionally, if there is a direct pathophysiological relationship between PH and CKD, the prevalence of pre-capillary PH should increase with the increase in the severity of the CKD. However, in this study, while the prevalence of post-capillary PH increased with worsening CKD, the prevalence of pre-capillary PH decreased. Hence, alternatively, it is possible that these are patients with either idiopathic or heritable pulmonary arterial hypertension who over time developed CKD due to right heart failure rather than CKD itself causing pulmonary vascular remodeling, albeit the severity of pulmonary vascular disease in this patient cohort is low.[7] The increased pulse pressure resulting from decreased vascular compliance exacerbates the renal disease progression.[8] Decreased pulmonary vascular compliance is a very early change in pulmonary hypertension.[9] Perhaps, decreased vascular compliance is a common pathophysiological change in both circulations in CKD. This might explain the increased occurrence of the pre-capillary PH in CKD.

Third, systemic hypertension is a well-established risk factor for developing PH, particularly due to heart failure with preserved ejection fraction.[10] However, in contrary, in this study, patients with PH and CKD were less likely to have systemic hypertension. The reason for this diverging observation is unclear. Also, the prevalence of chronic thromboembolic PH was not analyzed in this study.

Finally, this study fails to address a critical question, whether there is any cause and effect relationship between PH and mortality in patients with CKD, i.e. whether PH by itself causes increased mortality due to right ventricular failure or it is just a marker of the severity of the underlying comorbidities. This is important from a therapeutic perspective to determine whether PH should be a target of treatment in this patient population. A detailed echocardiographic analysis of right ventricular function and cause of death could have been obtained to address this important scientific knowledge gap.

In summary, O'Leary et al. provide a detailed hemodynamic characterization of PH in patients with CKD. This study also generates an exciting hypothesis that CKD by itself can cause pulmonary vascular remodeling. However, this needs to be tested in preclinical and clinical studies before it is widely embraced.

Conflict of interest

The authors declare that there is no conflict of interest.

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