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Commentary

Commentary on "Nephrectomy and High-Salt Diet Inducing Pulmonary Hypertension and Kidney Damage by Increasing Ang II Concentration in Rats"

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We read with great interest the study by Jiang et al. [1], which developed a novel rat model of chronic kidney disease (CKD)-associated pulmonary hypertension (PH) by a combination of 5/6 nephrectomy and a high-salt diet. This model successfully reproduced key features of CKD-PH, including altered hemodynamics and right ventricular (RV) hypertrophy. Importantly, Jiang et al. highlighted the overactivation of the renin-angiotensin-aldosterone system (RAAS) and reduction of angiotensin-converting enzyme 2 (ACE2) in pulmonary vascular endothelium as potential drivers of CKD-PH progression. However, the absence of distal pulmonary arteries remodeling and the exclusive use of male rats raises concerns about the model's accuracy or sex-difference in reflecting the full spectrum of CKD-PH pathophysiology. In this commentary, we discuss these limitations and propose considerations for refining the model to better reflect the condition of human CKD-PH.

PH is a serious cardiopulmonary condition, defined by the mean pulmonary artery pressure > 20 mmHg at rest [2,3]. Clinically, PH is categorized into five different types based on underlying etiologies [3]. The fifth group encompasses cases with unclear or multifactorial origins, including CKD-PH. This condition requires: (i) confirmation via right heart catheterization; (ii) two separate values of estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73 m^2 obtained at least 3 months apart [4]. Patients with coexisting CKD and PH are of significant clinical concern, given the consistent association between PH and worse outcomes in CKD patients [5]. Although clinical studies demonstrate a strong relationship between CKD and PH, the underlying biological mechanisms connecting the two conditions remain poorly defined [6–8]. Therefore, this gap highlights the need for appropriate animal models to investigate the intricate and multifactorial pathways contributing to CKD-PH.

In a recent study, Jiang et al. developed an innovative rat model of CKD-PH by combining 5/6 nephrectomy with 14 weeks of high salt dietary intervention [1]. This approach induced marked elevations in right ventricular systolic pressure (RVSP) and pronounced RV hypertrophy—two important indicators of PH pathophysiology. The model's novelty stems from its capacity to simultaneously capture the complex crosstalk between CKD and pulmonary vascular remodeling within a unified experimental system. Different from conventional CKD animal models, the 5/6 nephrectomy model [9] induces disease through blood volume overload and RAAS activation, whereas the adenine-induced model [10] relies mainly on the accumulation of uremic toxin and mineral metabolism disorders. In contrast, this model presented in Jiang et al.'s study integrates nephron loss with high-salt diet intake, to enhance angiotensin II signaling and RAAS overactivity, resulting in a more pronounced and clinically relevant manifestation of hemodynamic stress and right heart remodeling.

A notable aspect of this study is the observed dysregulation of RAAS and the reduced expression of ACE2 within the pulmonary arterial endothelium of CKD-PH rats. These alterations are consistent with established evidence regarding RAAS imbalance to vascular pathology, particularly in the context of cardiovascular disease and hypertension [11]. Notably, the excessive RAAS activity coupled with diminished ACE2 levels has been correlated with adverse outcomes in the pulmonary arterial hypertension (PAH) population [12]. Mechanistically, ACE2 can provide protective effects in pulmonary disease by mitigating the deleterious actions of angiotensin II [13]. Its regulatory role has made it

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a focus of therapeutic direction, with studies highlighting the consequences of ACE2 inhibition in preclinical research of PH studies [14,15]. Emerging evidence suggests that ACE2 expression could also be modulated post-translationally by murine double minute 2 (MDM2)-mediated modification of ubiquitination, potentially involving AMPK-MDM2 signaling crosstalk in PH pathogenesis [16]. Furthermore, overexpression of ACE2 has been shown to attenuate pulmonary artery remodeling [17], underscoring its promise as a potential therapeutic target in CKD-PH.

In addition to hemodynamic alternations, substantial metabolic irregularities were observed in this CKD-PH rat model, underscoring the systemic complexity of the disease. Serum metabolic profiling revealed significant deviations from control rats, including elevated levels of diacylglycerol (DAG), sphinganine, and other metabolites [1]. Notably, prior studies have implicated DAGs with angiotensin II (Ang II, hydrolyzed by ACE2)—dependent aldosterone release, offering a plausible explanation as a potential cause of raised DAG observed in this model [1,15,18]. These findings reinforce the view that CKD-PH, especially in more advanced stages, presents a multisystem disorder with complex metabolic involvement. The observed metabolic change points toward novel therapeutic opportunities, suggesting that interventions targeting lipid signaling and other metabolic pathways may be beneficial.

However, in contrast to the traditional PAH models such as the monocrotaline (MCT) and sugen5416/hypoxia rats model [19,20], this new CKD-PH rat model induced elevations in RVSP and RV hypertrophy without evident remodeling of distal pulmonary arteries. This discrepancy raises concerns regarding this model's ability to recapitulate the vascular pathology observed in human CKD-PH [21]. Distal pulmonary arteries remodeling increased pulmonary vascular resistance, contributing to increased pulmonary arterial pressure and subsequent RV failure [22,23]. This limitation highlights the need to refine this model further to reproduce better the vascular alterations seen in clinical cases. While the model effectively induces features of CKD and PH, the absence of pulmonary vascular remodeling represents a key shortcoming. Several potential explanations may account for this observation. First, CKD is known to induce systemic hypertension and heart failure, which can influence pulmonary hemodynamics and RV remodeling [24]. Second, the pathological process of CKD-PH likely involves multiple interacting mechanisms, including immune response or inflammation [25], oxidative stress [26], chronic hypoxia [27], and disturbances in calcium-phosphorus metabolism [28], which may contribute to pulmonary vascular calcification and further RV remodeling. Third, the 14-week observation period may have been insufficient to capture the complete temporal evolution of pulmonary artery remodeling. Prolonging the experimental duration or introducing additional pathological factors, such as hypoxia or sugen5416, may effectively develop the distal pulmonary arteries remodeling.

An additional limitation of this model involves its exclusion of sex differences by utilizing only male rats in this study. This omission holds particular significance given compelling evidence that sex-specific factors actively shape PH pathophysiology [29], particularly through modulation of aldosterone biosynthesis and hormonal signaling pathway [30]. For this novel preclinical CKD-PH model, evaluating whether female subjects develop distinct phenotypic manifestations is vital to strengthen its translational validity. Consequently, subsequent research should explicitly examine sex-based variations in both disease progression and underlying mechanisms.

In summary, this study meaningfully advances CKD-PH understanding by establishing a reliable rat model. While the absence of distal pulmonary vascular remodeling—a defining characteristic of human PH—constrains full translational applicability, this system nonetheless offers a useful experimental platform for mechanistic discovery and therapeutic evaluation. Enhancing clinical relevance will require refinement that better replicates human vascular pathology. Exploring contributors like chronic inflammation, oxidative stress, and sex-based specific differences could provide insights into the complex, multifactorial mechanisms in the context of CKD-PH. This work also highlights the role of RAAS imbalance and suppressed ACE2 expression as mechanistic features, which may serve as potential targets for further therapies to improve clinical outcomes in CKD-PH.

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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.

Statement of the Use of AI Tools

During the writing of this manuscript, the authors utilized generative AI tools (such as ChatGPT and DeepL) in order to improve readability and language. All conceptual development and final content decisions were made independently by the authors. After using these tools, the authors reviewed and edited the content as needed and took full responsibility for the content of the published article.

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