Pulmonary Arterial Hypertension and the Kidney: Getting to the Heart of the Matter

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The precise mechanisms underlying renal dysfunction in the setting of heart failure (HF) remain poorly understood. Until recently, the hemodynamic effects of the arterial side of the circulatory system were largely considered the key pathophysiologic pathway. The presumed interactions included a cascade of events starting with low cardiac output leading to a series of maladaptive hemodynamic and neurohormonal changes that ended in reduced glomerular filtration rate (GFR), and diminished ability of the kidneys to excrete excess sodium and water. However, several observations have challenged low forward flow as the principal or sole model linking the failing heart to the kidney, raising the possibility of alternative explanations [1]. There has been a growing interest in the role of the venous side of the circulation starting with high right atrial pressures (RAP) leading to renal venous congestion and its downstream impact on intra- and extra-renal hemodynamics as well as inflammation and endothelial activation (i.e., high backward pressure model) [2]. Accordingly, there have been several reports of GFR being correlated with high RAP and central venous pressure (CVP) but not with the cardiac index or left ventricular ejection fraction [3, 4]. Our current understanding of these pathophysiologic mechanisms is summarized in Figure 1.

Although studies underscore the clinical relevance of the pathways involving the right heart, they cannot provide mechanistic insights on the distinct role of arterial vs. venous side of the circulation as the origin of the pathways leading to renal dysfunction. They often include patients with various degrees of left cardiac dysfunction and fluid overload, hence making it difficult to disentangle the complex and interrelated mechanisms of the 2 sides of the circulation. In order to make such a distinction, a subset of patients are needed who present with predominantly high right-sided pressures at baseline, which are unrelated to left cardiac dysfunction or fluid overload; patients with pulmonary arterial hypertension (PAH) could be an ideal group. PAH, also referred to as group-1 pulmonary hypertension (PH), is a distinct form of pre-capillary PH defined by a mean pulmonary artery pressure >25 mm Hg in the presence of a pulmonary capillary wedge pressure ≤15 mm Hg. PAH is a progressive condition characterized by endothelial dysfunction and remodeling of pulmonary vascular medial and intimal layers resulting in constrictive and occlusive vascular lesions. The connective tissue diseases frequently associated with these PAH patients often have renal complications (e.g., in lupus, scleroderma), and this outcome complicates analyses of kidney dysfunction and treatments. In contrast to group-2

Fig. 1. Reciprocal pathways linking heart failure and renal dysfunction in cardiorenal syndrome. Decompensation of heart failure can lead to deterioration in renal function via low cardiac output, arterial underfilling, low perfusion, and exacerbated neurohormonal activity (i.e., low arterial forward flow-red circle) or through

fluid overload, venous distension, and renal venous congestion (i.e., high backward venous pressure-blue circle). LVEDP, left ventricular end-diastolic pressure; LVF, left ventricular function; IL-6, interleukin-6; TNF- α , tumor necrosis factor- α ; MCP-1, monocyte chemoattractant protein 1. Adapted with permission from Kazory [9].

PH, where the increased pressures of the right side of the heart are related to left cardiac dysfunction, patients with PAH do not have high left atrial pressures.

In this issue of the *journal*, Bitker et al. [5] present the results of an observational study on 179 patients with PAH exploring the factors associated with renal dysfunction. The study population had a cardiac index of 2.6 L/min/m² and an estimated GFR of 74.4 mL/min/1.73 m² at baseline; 29% of the patients had a GFR of less than 60 mL/min/1.73 m² at the time of the diagnosis of PAH. Over a follow-up period of 2.8 years, the authors observed a mean reduction of 0.85 mL/min/1.73 m² per year in GFR. Interestingly, high RAP and reduced cardiac index were both independently associated with a decline in renal function. Not surprisingly, renal dysfunction was associated with higher mortality in the study population.

How can we explain the findings of this study in the context of what we already know? First, in PAH where high right-sided pressures are pre-capillary and are not

secondary to left heart systolic or diastolic dysfunction, the low cardiac index did remain an independent risk factor for decline in renal function. This could in part be related to the high prevalence of renal dysfunction in these patients at baseline (hence, impairment in renal autoregulation) making them susceptible to injury even with milder decrease in cardiac output and renal blood flow. Second, similar to studies on patients with left-sided HF, the worst renal function was reported in those patients who experienced simultaneous low cardiac output and high RAP. This is reminiscent of the observation that in patients with acute decompensated HF, disproportionate increase in right to left ventricular filling pressures is associated with renal dysfunction independently of the RAP [6]. Interestingly, cardiac index turned out to be even a stronger marker than RAP for prediction of GFR. Third (and of special note), the investigators also observed significantly higher pulmonary arterial wedge pressures (representing left atrial pressures) in a subset of

patients who presented with very rapid decline in renal function (i.e., greater than 5 mL/min/1.73 m² per year reduction in GFR). These 3 observations lend support to each other; although the initial abnormality in PAH lies within the high pressures on the right side of the circulation, development of the left side dysfunction and post-capillary PH will be an add-on phenomenon later during the course of this progressive disease with further untoward impact on renal function.

So, while previous studies on predominant left-sided HF and volume overload point to high pressures on the right side as playing an important role in the development of impairment in renal function, interestingly the study by Bitker et al. [5] on patients with PAH emphasizes the key role of the left cardiac dysfunction. These observations highlight the intertwined bi-directional pathways linking the 2 sides of the circulation, and underscore the clinical relevance of renal perfusion pressure (as defined by the difference between mean arterial pressure and central venous pressure) for prediction of renal function in this setting. The pathophysiology is further complicated by the overlap of neurohumoral (sympathetic nervous and renin angiotensin aldosterone systems) and cytokine factors that cause pulmonary or renal injury: organ dysfunction in turn exacerbates these pathways and causes a vicious lung-kidney axis cycle.

These findings can have significant practical implications from a renal standpoint. Management of patients with PAH is conventionally focused on the reduction of the right side pressures with expected salutary effects on renal function such as those shown with sildenafil [7]; however, findings are difficult to interpret, since many of the pulmonary vasoactive medications also have direct salutary effects on the renal vasculature and may also impact extracellular matrix formation, nitric oxide, and apoptosis. Use of agents that are typically used for systolic HF (possibly associated with group-2 PH) and portend uncertain impact on renal perfusion pressure (e.g., neprilysin inhibitors) should be used with caution in the setting of PAH particularly in those patients with appreciable baseline renal dysfunction.

Besides hemodynamic factors, the role of other less well-studied mechanisms as the intermediary pathways through which PAH portends its adverse impact on renal function should also be considered. The study by Bitker et al. [5] did not explore the neurohormonal system or the markers of inflammation and endothelial activation. It has been proposed that venous congestion and increased venous pressures could change the endothelium from a quiescent redox profile to an activated proinflammatory,

pro-oxidant, and pro-vasoconstrictive state. In this regard, a number of molecules and signaling pathways have been proposed, mostly in animal studies, as potential mediators linking PAH to kidney dysfunction such as endothelin-1, interleukin-6, angiotensin-2, transforming growth factor-beta, bone morphogenic protein-2, and asymmetric dimethyl arginine [8]. There are apparent similarities between the pathophysiologic processes involved in PAH with those seen in the vasculature of patients with kidney disease (i.e., changes in arterial intima and media leading to increased vascular stiffness and resistance). As such, it remains to be elucidated whether these mediators indeed have a causative role or merely represent common pathophysiologic pathways in PAH and kidney dysfunction. Addition of novel serum and urine biomarkers of kidney injury and analysis of their correlation with the longitudinal changes in the right and left heart pressures are needed in future studies with longer follow-up periods to shed light on the complex interactions between the heart and the kidney in PAH. Moreover, incorporation of more objective measurements of fluid overload as well as newly marketed devices that allow continuous monitoring of intracardiac pressures are likely to help have a better understanding of the interplay between the cardiac function and renal impairment in this setting.

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