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EDITORIAL COMMENT

Renal Dysfunction in Heart Failure

The Role of Cardiac Afferent Fibers*

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Dynamic interactions among the heart, kidneys, vasculature, and autonomic nervous system intricately regulate blood volume, vascular tone, and cardiac output. These relationships are bidirectional such that acute or chronic disease in one system can strongly influence dysfunction of another. Cardiorenal syndromes are a heterogenous set of disorders classified by the primary underlying disease process and acuity to guide therapeutic strategies. In cardiorenal syndrome type 2 (CRS2), underlying primary chronic cardiac disease such as congestive heart failure (CHF) leads to chronic kidney dysfunction and is strongly associated with greater hazard of all-cause mortality in direct proportional to the degree of decline in renal function.[1] Conventionally, CRS2 has been attributed to impaired blood flow secondary to cardiac disease, resulting in renal hypoperfusion. In discordance with this, studies have demonstrated that renal function can decline in patients who are normotensive or those with no impairment in left ventricular (LV) systolic function. As a result, other mechanisms such as renal venous hypertension secondary to elevated central venous pressure, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, impaired natriuresis, and endothelial dysfunction have been implicated in the development of CRS2.

In this issue of *JACC: Basic to Translational Science*, Xia et al[2] studied the role of the cardiac spinal afferent reflex (CSAR) in the development of CRS2 in a rat model of CHF secondary to myocardial infarction (MI). Disruption of cardiac afferent fibers by epicardial application of resiniferatoxin (RTX) at the time of MI reduced the CSAR and ameliorated cardiac dysfunction. Importantly, renal dysfunction, as evaluated through urine output, microalbuminuria, and renal blood flow significantly improved with chronic cardiac afferent ablation compared to vehicle. This process was partly related to reduced central venous congestion, less cortical and medullary injury, and down-regulation of genes involved in inflammation, apoptosis, and hypoxia. Xia et al[2] further evaluated specific components of afferent and efferent components of the neural circuitry involved in the renal protection observed by cardiac afferent disruption. To evaluate whether the RTX-ablated cardiac afferent fibers travel through the stellate ganglia (SG), rats underwent RTX or vehicle injection into the bilateral SG 4 weeks after MI. The CSAR was significantly reduced compared to vehicle, and markers of renal dysfunction including blood urea nitrogen and renal *Kim1* expression were normalized, but cardiac function remained impaired. Finally, unilateral renal denervation (URDN) was performed at 4 weeks post-MI to evaluate potential contributions of afferent and efferent projections to the kidney. Compared with sham denervation, URDN improved LV function, glomerular filtration rate, and secondary markers of renal injury in bilateral kidneys.

Autonomic dysfunction has been implicated in the progression of most cardiovascular disorders, including CHF. The majority of existing medical therapies for CHF currently target the end-effectors through neurohormonal blockade such as β-blockers and angiotensin-converting enzyme inhibitors. Consistent with this, direct cardiac sympathetic nerve recordings in small mammals have identified greater

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basal sympathetic tone in the setting of CHF and increased norepinephrine spillover in patients with CHF and reduced ejection fraction (EF).[3] Disruption of transient receptor potential cation subfamily V member 1-positive fibers using epicardial RTX at the time of MI has been previously shown to mitigate myocardial structural remodeling in both rats and pigs, directly implicating afferent dysfunction in remodeling after MI.[4,5] The present work[2] expands further on this, identifying that cardiac afferents contribute to renal dysfunction post-MI, partly mediated through pathways involving the SG. Moreover, this study provides functional evidence that restoration of renal blood flow, either by URDN or epicardial RTX, improves renal function. Lastly, these studies reinforce the concept that the earlier targeted neuromodulation therapy is applied in a rationale fashion, the greater the efficacy.

Given the relevance of renal dysfunction in CHF, both medical and device-based therapies have been recently evaluated for potential renal protective effects. For example, sodium-glucose co-transporter 2 inhibitors, though initially studied for diabetes, have demonstrated a reduction in renal dysfunction in randomized trials for heart failure with reduced EF. Mechanistically, preclinical studies suggest that sodium-glucose co-transporter 2 inhibitors improve cardiomyocyte and renal metabolism, reduce cardiac structural remodeling, and reduce renal norepinephrine content. Moreover, catheter-based approaches to improve renal arterial inflow or reduce renal venous congestion are under clinical investigation and may impart benefit by improving renal perfusion.[6] The present work[2] highlights yet another therapeutic strategy for renal dysfunction after MI—targeting cardiac afferents.

One interesting component of this study was the time period selected for RTX intervention on the SG and URDN. No significant difference in LVEF or chamber size was evident compared to vehicle, suggesting that post-MI cardiac remodeling had been established by this 4-week time point. Regardless, RTX injection into bilateral SG at 4 weeks modestly improved markers of renal injury without affecting cardiac function, providing further evidence that CRS2 occurs (and may potentially be ameliorated!) via mechanisms independent of underlying cardiac function. On the other hand, URDN at 4 weeks led to mild improvements in LVEF and LV chamber size as well as renal function, possibly caused by effects on renin-angiotensin-aldosterone system activation, norepinephrine release, or multilevel reflex mechanisms involving both renal afferent and efferent fibers. Further studies to evaluate the impact of earlier URDN or cardiac afferent ablation through injection of RTX into the SG may help delineate the time course of cardiac and renal remodeling after MI. Moreover, studies in large mammals and in conjunction with existing medical therapy are necessary to fully define the translational potential of these approaches for cardiorenal syndromes.

In summary, renal dysfunction commonly occurs in patients with CHF and is strongly associated with all-cause mortality. Increasing evidence suggests that such renal dysfunction is not solely related to impaired hemodynamics that occur in CHF, but is partly attributable to maladaptive mechanisms such as metabolic stress, renin-angiotensin-aldosterone system activation, and, now, reflexive sympathoexcitation. This study provides early evidence that the CSAR leads to renal dysfunction post-MI, partly through afferent signaling pathways that involve the SG. Moreover, in rats, autonomic afferent ablation through epicardial or intrastellate RTX or URDN can improve renal function after MI-induced CHF. As such, this work by Xia et al[2] provides an exciting avenue for further study and informs possible therapeutic strategies.

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UCLA has patents developed by Dr Ardell relating to cardiac neural diagnostics and therapeutics. Dr Ardell is a co-founder of NeuCures, Inc. Dr Hadaya has reported that he has no relationships relevant to the contents of this paper to disclose.

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