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EDITORIAL COMMENT

The Early Intertwining of the Heart and the Kidney Through an Impaired Natriuretic Response to Acute Volume Expansion*

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An estimated 20 million Americans may have heart failure without overt symptoms (stage B and early stage C), yet this syndrome remains poorly understood, and therapeutic options are largely limited to lifestyle and risk factor modifications (1,2). Although therapy with neurohormonal blockers should be considered for these patients, unless contraindicated, this recommendation is predominantly extrapolated from studies with systolic heart failure patients having minimal signs and symptoms. Therapies for isolated diastolic dysfunction are lacking, even though nearly 50% of heart failure is attributed to impaired diastolic rather than impaired systolic heart function (3,4). Understanding the pathophysiology of these pre-clinical stages of the disease is crucial, as treatment success is often considered the relief or prevention of systemic (venous) congestion (5).

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Most studies focus on early stage underlying structural and molecular changes leading to failing myocardium, but less is known about its precise role in cardiorenal interactions as a prelude to overt signs and symptoms of heart failure. Historically, both symptomatic systolic and diastolic heart failure exhibit the tendency to retain water and salt, which is often explained by the cardiorenal and cardiocirculatory heart failure models (6–10). However, the intertwining of the cardiorenal and humoral responses to achieve sodium and fluid homeostasis remains poorly characterized in early heart failure stages. In this issue of the *Journal*, McKie et al. (11) reported the possible contribution of impaired renal cyclic guanosine monophosphate (cGMP) activation in generating natriuretic response during volume expansion in systolic or diastolic dysfunction patients without overt congestion. Their results suggest that the renal response to volume expansion is similarly impaired in both systolic and diastolic heart failure, leading to an inability to produce the compensatory increase in natriuresis seen in normal subjects. These observations support the concept that congestion may be driven predominantly by impaired renal reserve rather than by progressive cardiac insufficiency.

We congratulate the authors in their efforts to further elucidate the pathophysiology of heart failure as it relates to the vulnerability toward congestion. Nevertheless, it is important to recognize that while the authors described these subjects as being "pre-clinical," the average B-type natriuretic peptide (BNP) of 110 pg/ml and the majority of patients being treated with standard heart failure medications may reflect a population that already has some degree of underlying symptomatic cardiac involvement, despite being able to walk >450 m (i.e., they are already in stage C heart failure but with minimal symptoms). Their data underscore how incorrectly disease severity is identified based on clinical or echocardiographic judgment alone, which clearly overlooks underlying vulnerability. The results also imply that conventional signs and symptoms (even with systemic or imaging measures) may lack the sensitivity to identify vulnerability of such impaired renal reserve without the provocation of volume expansion.

Growing evidence has suggested that hypervolemia by itself, or at least the blunted reaction to hypervolemia, is independently associated with adverse outcomes (5). Several reports recently suggested increased venous pressure to be the culprit hemodynamic lesion to account for worsening renal function in chronic advanced heart failure patients (12,13). Indeed, an index event damages heart function, leading to a decreased effective arterial blood volume, which is detected by several mechanoreceptors in the left ventricle, aortic arch, and carotid sinus as well as the kidney's baroreceptorlike juxtaglomerular apparatus. Reduced receptor activation can lead to an increase in sympathetic outflow from the central nervous system, activation of the renin-angiotensin-aldosterone system, nonosmotic release of arginine vasopressin, as well as the stimulation of thirst (5,6). The resulting venous congestion will further impair renal function (12–14). Although venous congestion was notably absent in the present study according to the inclusion criteria, patients in the heart failure subgroups had higher natriuretic peptide levels and higher tissue Doppler E/E′ ratio, both indicative of at least some augmentation in intravascular filling pressures. Nevertheless, with volume

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expansion, these parameters were not significantly altered, even in the setting of systolic and diastolic dysfunction, emphasizing the large capacity that probably the venous bed, splanchnic circulation, and the kidneys can handle with regard to volume load before overt congestion occurs. In other words, volume expansion seems to be well tolerated in compensated heart failure patients despite a blunted renal reserve. It is therefore unlikely that the impaired renal response to volume expansion is linked to chronic elevation of venous pressures in the "pre-clinical" stages of heart failure.

In addition, these intriguing data challenge conventional wisdom that increased diuresis in response to volume expansion is mediated through sensitive detection of increased filling pressures in the heart or great vasculature. In fact, the discordance between cardiac performance and renal response to volume expansion challenges once more the notion that, in heart failure, hypoperfusion of the kidney as a result of poor forward flow is responsible for this blunted response. Rather, the subsiding homeostatic adjustments at the level of renal tubules may be the early defects that lead to progressive congestion. As a result, the search for pathologic mechanisms that trigger such defects should be the focus. Further studies are needed to investigate if this blunted response is primarily renal in origin and independent of the cardiac dysfunction or actually directly intertwined with the underlying cardiac abnormalities, perhaps as a result of renin-angiotensin-aldosterone system/sympathetic nervous system up-regulation.

Importantly, the impaired renal excretory response to volume expansion is rescued by exogenous subcutaneous recombinant human B-type natriuretic peptide (BNP) injections, again independent of the heart failure subtype (11). However, the degree of plasma and urinary cyclic guanosine monophosphate responses to BNP in normal subjects was still far greater than that observed in patients with heart failure, and may indirectly suggest that even an increase in the overall circulating "functional" BNP (through exogenous administration) might not completely overcome the blunted renal natriuretic response (rather than an absolute lack of sufficient circulating functional BNP). Whether defects in specific natriuretic peptide receptors or post-receptor mechanisms could account for these findings may warrant further investigation. However, one has to be careful how to interpret these results, as more than two-thirds of heart failure patients were taking neurohormonal therapy, which might have confounded the response to volume expansion as well.

These intriguing observations raise questions about our current management strategy for heart failure, especially in the early stages of the disease, which have been focused primarily on systemic neurohormonal blockade. These findings imply that potentiating the natriuretic peptide system might serve as an important therapeutic target to improve the failing cardiorenal interactions in heart failure before overt congestion ensues. The challenge is to identify treatment strategies that can selectively improve renal natriuretic responses, particularly in patients with diminished reserve. On the basis of insights from McKie et al. (11), it is perhaps more important to revisit the delicate balance that the kidney brings to the syndrome of heart failure.

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