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EDITORIAL COMMENT

Paradoxical Cardiorenal Responses Following Acute Vasodilator/Natriuretic Treatment in Presystolic Heart Failure

Should We Be Surprised?*

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The kidney is a regulatory organ and is focused on maintenance of fluid and pressure homeostasis. The kidney is equipped with many mechanisms by which to maintain volume homeostasis; it takes its cues, however, from its "marital partner," the heart, in many circumstances and especially when the heart is failing (1). The heart and the kidney communicate through hormonal and neural systems to maintain life and organ function. The kidney is especially sensitive to changes in sodium delivery and sudden blood pressure reductions, and thus 1 needs to distinguish between immediate and long-term responses to hemodynamic changes of the kidney. What is perceived as an adverse response initially may be a beneficial response chronically, especially if the cardiovascular response is positive.

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The current study by Wan et al. (2) in this issue of *JACC: Basic to Translational Science* describes the acute cardiorenal effects of combining tadalafil, a phosphodiesterase-5 inhibitor (PDE5i), with nesiritide, a recombinant human B-type natriuretic peptide (BNP), in response to acute saline volume expansion in participants with preclinical systolic dysfunction (PSD) and stages 2 and 3A chronic kidney disease (CKD). The authors hypothesized that this combination would enhance the cardiorenal response to volume expansion in PSD compared with a PDE5i alone. Unfortunately, this was not the case. All variables reflecting cardiac performance and related compensatory hormonal changes were favorable; renal response was not. Pre-treatment with tadalafil alone increased renal plasma, urine flow, and sodium excretion. In contrast, pre-treatment with tadalafil plus nesiritide decreased renal plasma flow, glomerular filtration rate, and urine flow. Hence, addition of human BNP altered the predicted renal response. Before discussing the reasons for this paradox, it is important to note that the participants received only 1 dose of tadalafil plus nesiritide or placebo before the acute saline volume expansion.

What are possible reasons for this response? First, we need to understand the neurohormonal changes that affect the heart and the kidney at this stage of heart failure in the presence of CKD. As the authors note (2), the neurohumoral profile of their cohort is reminiscent of those in the SOLVD (Studies of Left Ventricular Dysfunction) Prevention cohort; that is, mild activation of the natriuretic peptide system and no activation of the renin-angiotensin-aldosterone system. An impaired renal response to acute volume expansion in the patients with PSD compared with normal subjects is known. In addition, patients with left ventricular dysfunction who are asymptomatic or have Class II heart failure symptoms already have a decreased ability to augment plasma atrial natriuretic

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peptide in response to sodium loading and thus may retain sodium.

The importance of the natriuretic peptide system in response to volume expansion in PSD is further underscored by data from animal studies showing significant urinary retention when the natriuretic peptide receptor-A is blocked (3). In contrast, a study randomized 36 adults with preclinical diastolic dysfunction to receive subcutaneous BNP for 12 weeks versus placebo (4). This study reported an increase in urinary cyclic guanosine monophosphate (cGMP) and natriuresis at 12 weeks with volume expansion, an effect similar to that in subjects without underlying cardiac or kidney dysfunction.

Given the data from the current study (2), potential mechanisms for impaired renal response to acute volume expansion in patients with PSD include decreased plasma atrial natriuretic peptide levels, up-regulation of PDE5 leading to greater degradation of cGMP, down-regulation of natriuretic peptides in the kidney, and up-regulation of neutral endopeptidases leading to disruption of the homeostasis of natriuretic peptides with downstream effects within the nephron. This latter hypothesis seems most plausible based on data regarding cGMP levels in the combination group.

As the authors speculate (2), PDE5 metabolizes cGMP, a second messenger that leads to vascular smooth muscle relaxation and subsequent vasodilation. Renal cGMP plays an important role in modulating glomerular filtration rate (GFR) and natriuresis. Chronic PDE5 inhibition for 10 days in dogs with experimental heart failure accentuated the renal actions of exogenous BNP by maximizing the cGMP system (5). The renal effect of BNP and PDE5i were synergistic compared with BNP monotherapy. This suggests that PDE5 up-regulation may contribute to natriuretic peptide desensitization. Thus, there may be a role for combined chronic treatment using both PDE5i and BNP to maximize the benefits of endogenous and exogenous natriuretic peptides.

The divergent responses between the heart and the kidney in the study by Wan et al. (2) may also relate to acute hemodynamic accommodation to changes in blood pressure. Specifically, there was a large drop in systolic blood pressure within the normal range from 125 to 112 mm Hg that was not seen in the placebo group. This would have an acute effect of reducing the GFR and, to a lesser extent, reducing renal plasma flow, especially in the presence of CKD. This would contribute to decreased sodium delivery to the descending loop of Henle, and result in greater sodium reabsorption and thus less sodium excretion. Moreover, 1 should also note that although autoregulatory mechanisms in the kidney attempt to maintain a relatively constant GFR within the normal pressure range, acute reductions even within this range result in these homeostatic mechanisms being transiently overwhelmed until they re-establish homeostasis.

Taken together with previous data, this study (2) helps in understanding the acute changes imposed by modifying the natriuretic peptide system in the early stage of heart failure and has clinical and therapeutic implications. Use of sacubitril/valsartan, currently approved for the treatment of advanced heart failure with reduced ejection fraction, resulted in positive renal benefits when used chronically (6). However, it should be assessed in this earlier setting of heart failure because of its potentiating effects on the natriuretic peptide pathway.

Finally, these results should remind us not to make decisions about long-term outcomes from acute changes in kidney function, especially if they are understandable based on hemodynamic and neurohumoral changes. This is exemplified by the original reports 20 years ago of nephrotoxicity from angiotensin-converting enzyme inhibitors because there were acute increases of 20% to 30% in serum creatinine (1). Publication of the early reports resulted in a major hesitancy to use this class of medication in heart failure and CKD. However, use over the last 20 years has taught us that up to a 30% increase in serum creatinine translates into equal or better cardiovascular and renal outcomes. Thus, it must be remembered that the current study (2) of acute findings in the kidney may translate to beneficial long-term outcomes.

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