

Heart Failure With Preserved Ejection Fraction

A Kidney Disorder?

James C. Fang, MD

Heart failure with preserved ejection fraction (HFpEF) is a frustrating problem. Although stiffening of the heart is common and can be frequently demonstrated, other mechanisms have been implicated to account for the common symptoms of exertional dyspnea and intolerance. However, what remains common to eventually all patients with HFpEF is what defines heart failure clinically, namely, volume overload. Surprisingly, why there is avidity for salt and water in HFpEF remains largely unexplored.

In heart failure with reduced ejection fraction, consistent and predictable hemodynamic abnormalities lead to activation and sustained stimulation of neurohormonal systems that result in renal retention of sodium and water. Interruption of this cascade slows disease progression in the heart and reduces clinical events, such as heart failure hospitalizations, a clinical marker of salt and water retention.

In contrast, there is no unifying paradigm for the tendency toward volume overload in HFpEF. The centrality of neurohormonal activation in HFpEF as an explanation is debatable. First, most invasive hemodynamic studies of HFpEF (excluding pure forms of HFpEF such as restrictive cardiomyopathies) do not find low cardiac output or arterial underfilling, accepted stimuli for salt and water retention. Second, limited studies that have directly measured sodium and fluid avid neurohormones provide conflicting data. Moreover, although natriuretic peptides often are elevated, the magnitude of elevation is often modest, particularly when viewed relative to the degree of volume overload. Three, antagonism of multiple neurohormonal systems in HFpEF has failed to decrease heart failure (HF) hospitalizations, most of which are characterized by salt and water overload. If the organ that is ultimately responsible for regulation of salt and water is not responding to exogenous signals, is it possible that this organ has an intrinsic dysfunction that is responsible? Could HFpEF sit at the renal end of the cardiorenal syndrome spectrum?

Several observations suggest kidney dysfunction in the pathogenic processes leading to HFpEF. Renal insufficiency perpetuates systemic inflammation and oxidative stress, well-known instigators in cardiovascular disease. Importantly, the systolic (and diastolic) abnormalities in HF with reduced ejection fraction can be reversed with kidney transplantation despite the nearly ubiquitous presence of hypertension after transplant. These myocardial improvements also appear across a spectrum of ejection fractions after transplantation, although data specifically in HFpEF would be desirable. Abnormal kidney function is also likely required to produce salt-sensitive hypertension,¹ an almost ubiquitous companion to HFpEF in the older patient.

Ironically, patients with significant renal insufficiency often are excluded from HF studies despite the critical nature of the kidney in sodium and fluid balance and its plight in the presence of common HFpEF comorbidities, such as hypertension, diabetes mellitus, and aging. Although recent HFpEF trials have included patients with chronic kidney disease, the degree of renal insufficiency may underrepresent the severity of disease in the community. Moreover, assessment of kidney function using glomerular filtration rate may not properly gauge the kidney's ability to maintain fluid balance. For example,

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in a study by Damman and colleagues,² biomarkers of renal tubular dysfunction, including *N*-acetylglucosaminidase, neutrophil gelatinase-associated lipocalin, and kidney injury molecule-1, were commonly abnormal despite similar degrees of chronic kidney disease as assessed by glomerular filtration rate. Importantly, these changes were predictive of outcome as well. Similar studies in HFpEF are needed, but such observations suggest there is a **limited appreciation for tubular dysfunction in HF.**

Inappropriate salt and water retention is deleterious over time. Sodium and volume overload contribute to kidney and cardiovascular dysfunction in a **vicious cycle.** In animal models, a **high-salt diet results in hypertension, severe ventricular hypertrophy, and cardiac fibrosis, as well as proteinuria, glomerulosclerosis, and renal inflammation.** Importantly, these effects were **attenuated** with the **thiazide** diuretic, indapamide. Fluid overload may be even more important than the presence of hypertension itself. In patients with chronic kidney disease, cardiovascular events are more likely in those with modest degrees of fluid overload, with or without concomitant hypertension.³

Abnormalities in the kidney's ability to maintain sodium and fluid balance seem to **precede** the development of HFpEF, and this temporal relationship provides further circumstantial support that **renal injury** may be a **proximal insult.** Prospective registry data indicate that **subtle abnormalities in renal function presage** the development of HFpEF, but **not HF with reduced ejection fraction.** In the middle-aged community Dutch cohort studied in the PREVEND (Prevention of Renal and Vascular End-stage Disease) trial, baseline elevations in urinary albumin excretion and cystatin C (in addition to atrial fibrillation and female sex) increased the risk of new-onset HFpEF, but not HF with reduced ejection fraction. In the ARIC study (Atherosclerosis Risk in Communities), moderate to severe chronic kidney disease (eg, glomerular filtra-

tion rate <60 mL/min per 1.73m²), doubled the risk of incident HF.

Should the kidney be a target for therapy? Clinical trial evidence suggests that drugs that impact sodium excretion reduce incident HFpEF. In the ALLHAT (Anti-hypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial), the **diuretic, chlorthalidone,** was associated with **less incident HFpEF** over time in comparison with lisinopril, amlodipine, and doxazasin.⁴ It also is notable that **spironolactone,** a diuretic, **lowered the risk** of the secondary end point of HF **hospitalizations** (again predominantly attributable to volume overload) in the landmark HFpEF trial, **TOPCAT** (Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist) trial. Finally, newer agents applied to HFpEF **may improve outcomes by preserving kidney function.** In an analysis from the PARAMOUNT (Prospective Comparison of ARNI with ARB on Management of Heart Failure With Preserved Ejection Fraction) study, the combination drug, **valsartan/sacubitril,** **attenuated the decline in kidney function** and produced **declines in N-terminal pro-brain natriuretic** peptide as well as beneficial clinical outcomes.⁵ Moreover, recent interest in nitric oxide-GC-cGMP pathway in HFpEF could have important kidney-specific effects.

There seems to be **sufficient evidence** to suggest a putative **role for the kidney in HFpEF** as the **ultimate arbiter** of **volume overload** and therefore a potential starting point in a patient vulnerable to the deleterious effects of excessive salt and water retention. Whether a patient has or does not have demonstrable ventricular or vascular stiffness or other cardiovascular disease, the syndrome of volume overload confers further cardiovascular injury and risk and may perpetuate the condition of HFpEF in a **vicious cycle** (Figure). Strategies that specifically address sodium excretion seem to have an impact on both incident HFpEF and decreas-

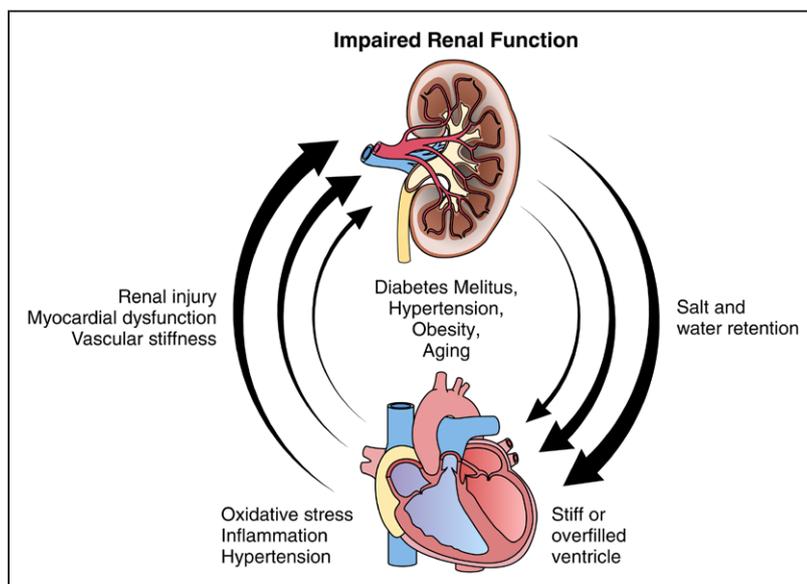


Figure. HFpEF as a vicious cycle of volume overload maintained by renal dysfunction. HFpEF indicates heart failure with preserved ejection fraction.

ing HF hospitalization. Perhaps volume overload is a modifiable risk factor that we can address to decrease the incidence and morbidity of HFpEF. Clearly, a more thorough understanding of the renal mechanisms of impaired sodium and fluid balance in HFpEF will be needed to lead to effective therapies in this heterogeneous syndrome. **Perhaps, it is time to consider HFpEF as a renocardiac syndrome.**

DISCLOSURES

None.

AFFILIATION

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FOOTNOTES

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Correction to: Heart Failure With Preserved Ejection Fraction: A Kidney Disorder?

In the article by Fang, “Heart Failure With Preserved Ejection Fraction: A Kidney Disorder?,” which published in the August 9, 2016, issue of the journal (*Circulation*. 2016;134:435–437. DOI: 10.1161/CIRCULATIONAHA.116.022249), several corrections are needed.

On page 435, the last full sentence on the page should read, “Moreover, assessment of kidney function using glomerular filtration rate may not properly gauge the kidney’s ability to maintain fluid balance.”

On page 436, the sentence beginning, “Abnormalities in the kidney’s inability...” should read, “Abnormalities in the kidney’s ability...”.

On page 436, the sentence beginning, “In the ARIC...” should read, “In the ARIC study (Atherosclerosis Risk in Communities), moderate to severe chronic kidney disease (eg, glomerular filtration rate <60 mL/min per 1.73m²), doubled the risk of incident HF.”

The publisher regrets these errors. The corrections have been made to the current online version of the article, which is available at <http://circ.ahajournals.org/lookup/doi/10.1161/CIRCULATIONAHA.116.022249>.

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