Renal Function and Heart Failure Treatment
When Is a Loss Really a Gain?

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A number of studies have demonstrated a linkage between renal dysfunction and adverse clinical outcomes in both acute and chronic heart failure.1–3 Heart failure treatments can affect renal function in a variety of ways, with decreased glomerular filtration rate (GFR) during treatment often denoting a poorer prognosis.4–6 Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) reduce GFR through intrarenal mechanisms yet convey reduced rates of morbidity and mortality, presenting the hypothesis that the association between change in GFR and clinical outcomes depends on the factors that drive that change more than on GFR itself. In this issue of Circulation: Heart Failure, Testani et al present evidence that supports this hypothesis, showing that within the SOLVD (Studies of Left Ventricular Dysfunction) study, early reduction in GFR was associated with increased mortality within the placebo group but not in the enalapril group. It is reasonable to conclude that inhibiting the renin-angiotensin system (RAS) reduces GFR through a mechanism that does not convey an adverse prognosis. In evaluating new therapies, focus should be placed on clarifying the pathways through which agents influence renal function.

Within the SOLVD study, despite exclusion of patients with serum creatinine of >2.0 mg/dL, baseline renal impairment was associated with reduced survival.2,3 Patients randomized to enalapril showed slight, but statistically significant mean increases in serum creatinine during treatment relative to those receiving placebo.6 There exist a number of putative mechanisms whereby heart failure therapies may influence renal function. Diuretics may predispose to prerenal azotemia through intravascular volume depletion, excessive cardiac preload reduction, and a resulting reduction in cardiac output. Loop diuretics also induce intrarenal mechanisms for reducing GFR, principally through adenosine release and diminished glomerular blood flow and filtration pressure, through A1-receptor stimulation.10 On the other hand, diuretics may augment cardiac output by reducing functional valvular regurgitation and diminishing ventricular interde-
GFR is a marker of worse heart failure and, thereby, is associated with worse outcomes. As depicted in Figure A, heart failure may reduce GFR directly through hemodynamic impairment (eg, reduced cardiac output or increased central venous pressure) or through kidney injury. The former is likely to be reversible with heart failure treatment, whereas the latter is likely to be irreversible. Heart failure treatments may similarly reduce GFR through reversible or irreversible mechanisms. Although unproven, it is reasonable to hypothesize that irreversible kidney injury is more likely to contribute directly to reduced survival than is reversible, hemodynamically mediated reduction in GFR.

Figure B depicts ways in which RAS inhibition may affect these interactions. In the absence of severe reduction in renal perfusion, as may occur with bilateral renal artery stenosis, RAS inhibition does not cause kidney injury. Rather, it induces a dose-dependent, reversible, hemodynamically mediated reduction in GFR. This effect may contribute directly to renal preservation as has been demonstrated in patients with diabetic nephropathy. As Testani et al suggest, the lack of association between early reduction in GFR during enalapril administration and subsequent mortality may signify that reduced GFR per se has no adverse impact on survival. However, even if GFR does have a direct impact on survival, when this effect occurs in the setting of ACEI initiation, any adverse effect may be offset by the direct survival benefit of this agent. It is striking that among patients continuing the study drug in SOLVD, greater survival benefit of enalapril versus placebo was observed in patients with early worsening of renal function. This finding suggests that during ACEI initiation, either reduced GFR is somehow directly linked with improved survival or, more likely, GFR reduction is a marker of greater RAS inhibitory effect with a resulting greater survival benefit.

The presumption of a causal linkage between renal function and subsequent outcomes, or the categorization of renal impairment as an important clinical outcome in its own right, has led to the exploration of drugs that improve GFR or preserve renal function in the setting of diuretic treatment. In this regard, inhibitors of the adenosine A1-receptor have held promise. Enthusiasm for this direction was dampened when the phase III PROTECT (Placebo-Controlled Randomized Study of the Selective A1 Adenosine Receptor Antagonist Rolofylline for Patients Hospitalized With Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function) study failed to confirm clinically relevant benefit with such an agent. Nevertheless, the opportunity of pharmacological renal protection remains, partly because renal impairment limits the use of other treatments, such as diuretics and RAS inhibitors, including aldosterone receptor blockers. Additionally, agents should be sought that prevent renal injury, as determined by the impact on markers such as neutrophil gelatinase-associated lipocalin, rather than on functional measures, such as GFR, alone.

Clearly, modest reduction in GFR associated with initiation of RAS inhibitors should not be viewed as carrying an adverse prognosis and should not be cause for drug discontinuation. On the contrary, it is a marker of pharmacological effect associated with this salutary treatment modality. Future research should be directed toward adding to the important insights provided by Testani et al and further deciphering the complex interdependencies among heart failure severity, treatment effects, renal function, and survival. Such insights will yield more cogent directions for drug discovery and investigation in both acute and chronic heart failure.

Disclosures

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References


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