Editorial Comment

# Treating the Cardiorenal Syndrome: A Sledgehammer for a Needle's Work?

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When providing care for the patient with advanced heart failure (HF), both diuretic resistance and worsening renal function (ie, cardiorenal syndrome) are common occurrences associated with poor outcomes.[1,2] When the rise in intravascular volume in decompensated HF exceeds the venous bed compliance, a venous backpressure in the kidney will occur. The ability of the kidneys to excrete salt and water in decompensated HF is to some degree related to this venous backpressure out of the kidney as well as the forward arterial perfusion into the kidney. As a result, interventions to address the cardiorenal syndrome have focused on 2 broad approaches: neurohormonal manipulation within the microvascular renal bed or manipulation of large-vessel renal hemodynamics (ie, increasing arterial flow and/or decreasing venous pressure).

Activation of the renin-angiotensin aldosterone (RAAS) and sympathetic adrenergic (SAS) systems is a fundamental component of the deleterious systemic effects observed in decompensated HF.[3] It is an important driver of cardiorenal syndrome (type 1), in which worsening HF leads to changes in intrarenal hemodynamics.[4] An increase in renal sympathetic nerve activity and systemic RAAS activation leads to renal vasoconstriction and a local decrease in renal blood flow. Data are mixed regarding whether high doses of loop diuretics, often used in cases of worsening HF, lead to greater RAAS and SAS activation.[5,6] Although there exists an association of worse outcomes with greater doses of loop diuretics in decompensated HF,[7] there is no definitive causal relationship between dose and cardiovascular mortality. Beyond diuretic therapy, the widespread use of ultrafiltration has been limited by results from trials including CARRESS-HF,[8] which demonstrated a higher rate of serious adverse events in those patients undergoing ultrafiltration in the setting of worsening renal function. Few alternate therapies are available as patients reach the end stage of cardiorenal disease beyond dual-organ transplantation.

Manipulation of large-vessel flow in and out of the renovascular bed is another potential strategy for mitigating worsening renal failure in decompensated HF. Device therapies such as continuous aortic flow augmentation (CAFA) to increase flow within the large-vessel arterial system have demonstrated efficacy in improving hemodynamics (increasing cardiac index and reducing pulmonary capillary wedge pressure) with reductions in serum creatinine and increases in urine output.[9,10] However, when CAFA was studied in a cohort of patients with decompensated HF compared with medical therapy alone, this intervention did not reduce the incidence of renal failure or death.[9] It is possible that this device was not effective in a randomized comparison because of patient selection; the patients may have been too ill to derive a benefit. Perhaps there is an earlier "sweet spot" in the trajectory of HF where such an intervention may be effective in the cardiorenal cascade. Given this hypothesis, it is possible a mechanical intervention at the right time in a patient's HF journey could potentially mitigate the cardiorenal syndrome.

It is with this background that Dierckx et al now present their early experience evaluating a novel device (Doraya catheter) percutaneously positioned in the inferior vena cava to purposefully obstruct venous flow.[11] The desired result of this device is to reduce renal venous congestion as well as to unload the left ventricle. The authors present the results of 2 patients who underwent this intervention after experiencing signs and symptoms of fluid overload with concurrent diuretic resistance. In both cases, the patients experienced a remarkable increase in urine output as well as decreases in left and right-sided filling pressures. As reported, the device itself can be used for up to 24 hours. The authors do not report any adverse events in these 2 cases and an ongoing larger study will further detail safety as well as hemodynamic effects.

This report is meaningful in demonstrating that a short-term mechanical intervention can acutely reduce both cardiac and renal congestion. Moreover, it confirms prior

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observations that backpressure in the kidney is related to diuretic response and that relief of this backpressure can improve diuretic responsiveness. Specific mechanisms cannot be gleaned from this report but acute local changes in the neurohormonal milieu, a decrease in renal interstitial pressure, increases in cortical relative to medullary blood flow, and increased filtration pressure across the glomerulus may all play roles.[12] Patient selection, safety, durability of the response, disease modification, and overall patient experience remain important issues to resolve. Moreover, congestion in HF is a symptom of a problem—when the stimulus for sodium and fluid retention is powerful, the kidney is enormously resistant to manipulation and overcoming its avidity for volume will not be as simple as changing backpressure to the renal bed.

Finally, as we have seen in many contemporary device trials in cardiology, consideration of a sham-control study will need to be debated.[13] Despite the obvious hurdles, we would encourage consideration of blinding into the study design, particularly if more preliminary data support a broader trial. Importantly, we would be remiss in not congratulating the investigators for thinking creatively and "out of the box" for this large unmet need. We look forward to hearing more about this intriguing idea and whether or not mechanical solutions to a biologic problem will work.

## References


1. Smith GL, Lichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, Krumholz HM. Renal impairment and outcomes in heart failure: systematic review and meta-analysis. J Am Coll Cardiol 2006;47:1987–96.
2. Verbrugge FH, Mullens W, Tang WH. Management of cardio-renal syndrome and diuretic resistance. Curr Treat Options Cardiovasc Med 2016;18:11.
3. Braunwald E. JACC Heart Fail 2013;1:1–20.
4. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol 2012;60:1031–42.
5. Mentz RJ, Stevens SR, DeVore AD, et al. Decongestion strategies and renin-angiotensin-aldosterone system activation in acute heart failure. JACC Heart Fail 2015;3:97–107.
6. Felker GM, O'Connor CM, Braunwald E. Loop diuretics in acute decompensated heart failure: necessary? Evil? A necessary evil? Circ Heart Fail 2009;2:56–62.
7. Hasselblad V, Stough WG, Shah MR, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE Trial. Eur J Heart Fail 2007;9:1064–9.
8. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. N Engl J Med 2012;367:2296–304.
9. Greenberg B, Czerska B, Delgado RM, et al. Effects of continuous aortic flow augmentation in patients with exacerbation of heart failure inadequately responsive to medical therapy: results of the Multicenter Trial of the Orqis Medical Cancion System for the Enhanced Treatment of Heart Failure Unresponsive to Medical Therapy (MOMENTUM). Circulation 2008;118:1241–9.
10. Konstam MA, Czerska B, Böhm M, et al. Continuous aortic flow augmentation: a pilot study of hemodynamic and renal responses to a novel percutaneous intervention in decompensated heart failure. Circulation 2005;112:3107–14.
11. Dierckx R, Vanderheyden M, Heggermont W, et al. Treatment of diuretic resistance with a novel percutaneous blood flow regulator: concept and initial experience. J Card Fail 2019;25:932–4.
12. Ross EA. Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. J Card Fail 2012;18:930–93.
13. Prasad V, Cifu AS. The necessity of sham controls. Am J Med 2019;132:e29–30.