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EDITORIAL COMMENT

# The Fastest Way to the Failing Heart Is Through the Kidneys*

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It might be difficult for some to acknowledge, but heart failure cardiologists need to be specialized nephrologists. The large majority of pharmacological therapies we have developed in the last decades to improve clinical outcome in patients with heart failure and a reduced ejection fraction act on the disproportional neurohormonal activation leading to renal salt and water retention in heart failure. As such, heart failure cardiologists treat the heart by treating the maladaptive responses that occur in the kidneys. Therefore, knowledge of the renal pathophysiology and pharmacodynamics of therapies used in heart failure is essential for heart failure specialists to guide individual treatments.

Although the association between renal dysfunction and worse outcomes in patients with heart failure is well-established, it is increasingly important to evaluate changes in renal function during initiation of evidence-based therapies, during decongestive therapies, and probably as routine measurement as well (1). Furthermore, there is evidence that heart failure patients experience tubulointerstitial damage and albuminuria, similar to patients with primary nephrologic disorders, although the pathophysiology might be entirely different. Most importantly, reduced glomerular filtration rate (GFR), and possibly tubular dysfunction, which is responsible for sodium and water homeostasis, is primarily determined by impaired renal hemodynamics. A reduced renal blood flow, sometimes in combination with an increase in central (and renal) venous pressure, has been shown to be the primary determinants of renal impairment in heart failure (2,3).

Central hemodynamics are reasonably easy obtainable in patients with heart failure by insertion of a pulmonary artery catheter, which will give an estimate of cardiac output and central venous pressure (CVP). However, how these differences in central hemodynamics in patients with heart failure translate into differences in intrarenal hemodynamics is not easy to determine. Assessment of renal blood flow is time consuming and patient unfriendly due to its invasive nature and the use of radioactive tracers. Direct measurement of renal venous pressures could be feasible by the insertion of a pressure catheter, but this technique also has limited applicability due to its invasive nature and need for fluoroscopy. In a way, the kidney presents itself as a "black box" in patients with heart failure: we can get some idea of the end product (GFR and diuresis), but what the content of the box is, and how it responds to therapy and hemodynamic alterations, is largely unknown.

SEE PAGE 672

The paper by Nijst et al. (4) in this issue of *JACC: Heart Failure* contributes to our understanding of this black box. Their research focused on the noninvasive assessment of estimates of renal arterial and venous flow patterns as assessed by echography. The authors are not the first to describe these flow patterns and how they behave in patients with heart failure, but their investigations give some intriguing insights into hemodynamic and renal adaptive responses during volume loading and unloading in heart failure. Nijst et al. (4) started off with presumably euvolemic patients with heart failure and a reduced ejection fraction and patients with heart failure and a preserved ejection fraction with relatively preserved renal function (estimated GFR around 60 ml/min/1.73 $m^2$)

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and subjected these patients (and controls) to a total of 1 liter fluid expansion over 3 h, followed by fluid unloading by intravenous bolus of bumetanide. Their first observations on the baseline renal Doppler measurements in heart failure patients confirm what has previously been shown; in compensated heart failure patients, a continuous venous flow pattern is observed, which largely resembles the normal situation; this pattern was also found in control subjects. After infusion of fluids things got more interesting. In patients with heart failure and a reduced ejection fraction and patients with heart failure and a preserved ejection fraction, a majority of patients developed a biphasic pattern of the venous impedance index, in contrast with control subjects where no alternations where observed. This biphasic intrarenal venous flow pattern has recently been shown to be prognostically unfavorable in patients with heart failure (5). The current hypothesis, based on findings by Nijst et al. (4) and Iida et al. (5) both published in *JACC: Heart Failure* is that the biphasic, discontinuous venous flow reflects a decrease in intrarenal venous compliance, an increase in renal interstitial pressures, and could reflect an increase in right-sided cardiac filling pressures (4,5). The latter is supported by the finding that the lower venous impedance index is probably predominantly related to lower maximum flow velocity at the nadir, which was more often zero after fluid expansion in the study conducted by Nijst et al. (4). Because this nadir directly follows after the (right) atrial contraction, it is tempting to speculate that more prominent pressure waves generated by the right atrium in response to fluid expansion, transmit directly and more pronounced to the renal venous vasculature in patients with heart failure compared with control subjects. This difference with control subjects is probably a reflection of these mechanisms, namely decreased venous compliance due to increased CVP and increased renal interstitial pressures.

The research by Nijst et al. (4) helps us to better understand intrarenal venous flow patterns in patients with heart failure and gives some insight in the association with diuretic response. However, we should be careful in extrapolating these findings to the acute heart failure population where assessment of congestion and intrarenal venous flow patterns may be most interesting. Whereas the heart failure patients who were studied were euvolemic at baseline, had relatively low CVP, and preserved estimated GFR, acute heart failure patients are characterized most often by strongly increased CVP, high blood pressures, lower estimated GFR, and greater intra-abdominal pressures. How these factors and the additional effect of decongestive therapies influence the changes in intrarenal venous flow patterns is difficult to predict and should be the focus of future studies. Also, assessment of intrarenal venous flow patterns in the often critically ill, dyspneic patient with acute heart failure will be more challenging, limiting its usability. Furthermore, to date it is unclear whether abnormal intrarenal venous flow patterns in the long term may influence intrarenal hemodynamics and renal function, or influence the response to diuretic therapies. Finally, whether assessment of these intrarenal flow parameters may help to determine starting or stopping, intensifying or decreasing diuretic/decongestive therapies should be the focus of future studies.

It is, however, clear that the lid on the black box surrounding the intrarenal hemodynamics in heart failure has been opened, and bit by bit we are beginning to understand more and more about how individual differences in intrarenal hemodynamics and function may alter the response to decongestive and evidence-based therapies. Therefore, more research should be focused on intrarenal pathophysiology in heart failure as it increasingly recognized that the fastest way to the failing heart is through the kidneys.

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