Cardiac Output and Renal Dysfunction
Definitely More Than Impaired Flow*

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Patients with heart failure (HF) now rarely present in cardiogenic shock. Instead, HF has become a chronic systemic disease in which symptoms and disease progression are related to unrestrained neurohumoral stimulation, leading to water and sodium retention (1). Because the kidneys are responsible for fluid homeostasis, it is not surprising that renal function is one of the strongest predictors for outcome in HF, outperforming other prognosticators that directly reflect cardiac function (2). The interdependence between the heart and the kidneys has been a topic of extensive research for decades. Intuitively, progressive renal dysfunction is often attributed to hypoperfusion of the kidney due to progressive impairment of cardiac output. However, a drop in systemic blood pressure, venous congestion, and intra-abdominal pressure are hemodynamic parameters stronger associated with worsening renal function in heterogeneous populations with HF (3–6).

In this issue of the Journal, Hanberg et al. (7) provide further data to support the disconnect between cardiac output and renal function in a HF population with careful cardiac and hemodynamic profiling. They concluded a post hoc subanalysis from the randomized and registry portions of the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheter Effectiveness) trial to specifically evaluate the association between cardiac output and renal function (7). The study population consisted of patients with advanced heart failure with a reduced ejection fraction (mean ejection fraction 23 ± 12%) with an average cardiac index (CI) of 2.3 ± 2.1 l/min/m² and a right atrial pressure of 14 ± 9 mm Hg. The authors investigated the correlation between CI and renal function in the combined study cohort (>500 patients), as well as across specific well-characterized subgroups in which reduced cardiac output was expected to play an important role (i.e., high right atrial pressure, more impaired renal function, or low systolic blood pressure). Overall, no positive association between CI and renal function was found. Therefore, this analysis is consistent with previous data, and together with the finding of a lack of success of treatment strategies focused at improvement of renal function through enhanced cardiac output, it is evident to conclude that a reduced CI is not a hemodynamic driver for renal dysfunction in patients hospitalized for HF who are not in shock. To better appreciate these findings, a brief review of cardio-renal physiology might be insightful.

glomerular filtration is not the sum of hemodynamic factors

The kidneys preserve the fluid and electrolyte balance of the body to protect tissue perfusion, as well as intra- and extracellular volume homeostasis. To do this, the kidneys must filter a sufficient, and rather fixed, amount of blood per time from the renal glomerular capillaries into the Bowman’s capsule (filtration function) and precisely regulate tubular water and solute reabsorption (tubular function). Renal blood flow (RBF) is normally approximately 20% of the cardiac output and determined by the difference between renal arterial and venous pressure, the intra-abdominal pressure, and the tonus of the renal vasculature (3,4,6,8). The glomerular
filtration rate (GFR) depends on RBF, but more importantly on Starling forces between the glomerular capillaries and Bowman’s space. Importantly, due to the essential role of the kidney, the human body possesses extensive mechanisms to preserve GFR. First, an important decrease in cardiac output will lead to a redistribution of blood volume within the body to preserve kidney perfusion. Second, intrinsic autoregulation mechanisms will keep the GFR within narrow limits within the kidney (Figure 1). Therefore, GFR is a complex interplay of hemodynamic factors and autoregulation mechanisms.

**FILTRATION FRACTION AND TUBULAR SODIUM AVIDITY: THE BIGGER PICTURE**

Although it seems appealing to finally end the tale on cardiac output and renal function, the bigger picture should not be missed. GFR has proven to be a very important prognostic marker, but it is probably

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**Figure 1: FF Is More Important Than GFR in Heart Failure**

Glomerular filtration rate (GFR) is kept constant over a wide range of renal arterial perfusion pressures by adapting the resistance of the afferent (adenosine) and efferent arteriole (renin). Therefore, comparable levels of GFR can reflect different situations. When renal perfusion is low, GFR is preserved, resulting in an increase of the filtration fraction (FF). This leads to higher oncotic and lower hydrostatic pressure in the peritubular capillaries, strongly facilitating sodium (Na⁺) and water reabsorption. The increased reabsorption of sodium in the proximal tubule reduces its availability to the macula densa, further stimulating renin release, which will increase the FF even more. Also, distal tubular flow will be lower, which enhances the response to aldosterone and impairs the action of natriuretic peptides (9). RAAS = renin-angiotensin aldosterone system.
not a good target to improve outcome. Moreover, during effective decongestion and up titration of renin-angiotensin blockers, a small GFR decrease has been associated with improvement in survival and less re-admissions for HF (10,11).

As the body aims to preserve GFR, the filtration fraction (FF), which is the ratio of GFR/RBF, will be altered. As a result, 2 comparable levels of GFR can reflect a different situation (Figure 1). When the FF is increased, a state of high water and sodium avidity, which is characteristic of HF, is induced. This results in high proximal tubular sodium reabsorption enhancing neurohumoral activation and resistance to the action of natriuretic peptides (Figure 1) (9). Therefore, any strategy that intends to lower the FF or targets sodium reabsorption in the proximal tubules may have large benefits in decompensated HF. For example, renin-angiotensin blockers, which mediate efferent arteriolar vasodilatation, and therefore, cause an increase in RBF and a decrease in FF, have been proven to lead to increased diuretic and natriuretic capacity in chronic and acute HF, even in the face of a potential drop in GFR (12). Serelaxin, a recombinant human relaxin-2 and acute HF, even in the face of a potential drop in RBF and a decrease in FF, have been proven to lead to angiotensin blockers, which mediate efferent arteriolar vasodilatation (17).

A lthough results so far large port(15,16) . These drugs should enhance distal tubular diuretic responsiveness (17). Interestingly, the increase in RBF (up to 50%) is significantly reduces rehospitalization and short-term mortality in acute HF (secondary endpoints) and preserves renal function, increases RBF and reduces FF, but does not significantly affect GFR (13). Interestingly, the increase in RBF (up to 50%) is probably related to a reduction in venous congestion and vasodilatation of the afferent and efferent arteriole unloading the glomerulus (14). Furthermore, acetazolamide, an old and largely forgotten diuretic, and sodium-glucose transporter-2 (SGLT-2) inhibitors, which recently demonstrated striking effects on cardiovascular endpoints in patients with type 2 diabetes mellitus, both inhibit proximal tubular sodium transport (15,16). These drugs should enhance distal tubular flow in the nephron that counteracts salt retention, facilitates decongestive treatment and boosts loop diuretic responsiveness (17). Although results of large randomized clinical trials are not yet available, these therapeutic strategies look very promising.

Finally, an important obstacle in optimizing decongestive strategies in HF and the major shortcoming of the study of Hanberg et al. (7) is that only metrics of renal filtration function were analyzed. Surely, GFR is an estimate of the renal “reserve” available to relieve congestion and to respond to the insult posed by HF. However, GFR, based on serum creatinine, is an inaccurate reflection of only the filtration function of the kidney, whereas other components, such as renal tubular avidity for fluid and sodium, are not revealed. Currently, loop diuretic response, defined as sodium output over loop diuretic dose, may be one of the best markers of the cardio renal interaction, because it better reflects the renal reaction to volume status on the filtration and tubular level (18). However, practical difficulties with urine analysis, and failure to identify the specific etiology and best treatment strategy in case of a poor response lack clinical use. Recently, a urinary spot analysis after administration of a diuretic agent has been investigated, which excellently reflected a natriuretic response and might make an individualized approach in HF patients feasible (19).

In conclusion, the results in Hanberg et al. (7) convincingly show that renal filtration function during acute HF is not driven by changes in cardiac output. Future research should focus on other metrics of renal function to diagnose a state of increased water and salt avidity. Meanwhile, the principal target for the treatment of acute HF patients must remain efficient decongestion and restoring a neutral salt and water balance without specifically wanting to improve cardiac output.

**REFERENCES**


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