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EDITORIAL COMMENT

Looking at the clock of kidney dysfunction

O relógio da disfunção renal na insuficiência cardíaca aguda...

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Heart and kidney walk side by side along the path of heart failure (HF). Chronic kidney disease (CKD) is highly prevalent and has a similar impact on prognosis among HF patients regardless of ejection fraction. CKD is present in up to 50% of HF patients and increases their risk of death to 25% at one year. HF patients with CKD are normally older, have more comorbidities and are more symptomatic than HF patients without CKD.[1,2]

The complex hemodynamic and neurohormonal interaction between the heart and kidney gave rise to the concept of the cardiorenal syndrome, in which dysfunction of one organ induces or aggravates dysfunction in the other, impacting on each other's prognosis.[3] Renal dysfunction in HF is a consequence of the complex interaction between hemodynamic factors, systemic congestion, inflammation, endothelial dysfunction, and neurohormonal mechanisms. A reduction in cardiac output in patients with chronic HF has been shown to result in a decrease in renal blood flow, activating renal mechanisms that result in water and sodium retention and thereby causing congestion. This congestion further worsens HF but also leads to an increase in central venous or abdominal pressure, which ultimately causes worsening renal function (WRF).[4]

In acute heart failure (AHF), congestion is the main clinical presentation, and therefore WRF is prevalent among AHF patients. In their study published in this issue of the *Journal*, Presume et al. assess the prognosis of AHF patients according to the time of WRF onset.[5] Unlike the majority of works on this subject, the authors aim to identify the prognostic value of WRF according to the time of its occurrence during a HF decompensation episode. WRF was defined as an increase in serum creatine (SCr) of >0.3 mg/dl. If WRF occurred within the six months before admission, it was classified as acute kidney injury (AKI). During hospitalization for HF, WRF was analyzed in patients with or without AKI at admission, who were classified as having early (≤48 hours) or late (>48 hours) WRF. Studying a total of 249 patients, of whom 62.2% had preserved left ventricular ejection fraction and 55.8% had CKD, the authors found that WRF was a stronger predictor of worse prognosis at one year (hazard ratio [HR] 1.69; 95% confidence interval [CI] 1.15–2.48; p=0.007). In particular, early WRF was associated with a significantly higher incidence of the primary outcome (HR 2.49; 95% CI 1.66–3.73; p<0.001), whereas late WRF was not (HR 0.80; 95% CI 0.45–1.40; p=0.411), compared to patients who did not develop WRF. The outcome at one, three and six months was also worse for patients who developed early WRF, as length of hospital stay was longer. Interestingly, AKI at admission was not an independent predictor of the primary outcome.[5]

These results illustrate common beliefs concerning the prognostic impact of WRF in AHF patients. Nevertheless, the evidence is conflicting, and some studies show that WRF during hospitalization for HF is a less important predictor of events than AKI at admission.[6,7] Others, even from the same

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authors, emphasize the impact of early AKI during hospitalization for HF.[8] But in all these works, the time frame for recording the onset of WRF during hospitalization for HF was longer, around five days after admission. Also, the prevalence of HF patients with preserved ejection fraction (HFpEF) in these studies was considerably lower than in the present study population, in which HFpEF prevalence was 62.2%.[5–7]

In Presume et al.'s study, WRF during hospitalization for HF was more important than AKI at admission, and early WRF was the main predictor of post-discharge prognosis.[5] This may reflect the different pathophysiological mechanisms of WRF during AHF, of which intra-abdominal (visceral and/or renal) congestion may be among the most important.[4] Prompt diuretic therapy for decongestion or improvement of perfusion by increasing cardiac output are the strategies for congestive patients (warm-wet [type B] and cold-wet [type C] hemodynamic profiles). Improvement of AKI present at admission is the most frequent result of an efficacious decongestive approach to the AHF patient. Unfortunately, effective decongestion is difficult to achieve and WRF arises as congestion persists or worsens. One possible explanation for Presume et al.'s results is that early WRF is a marker of unsuccessful decongestion and is therefore associated with a worse prognosis. By contrast, late WRF may reflect the effects of diuretic therapy leading to excessive reduction of preload and systemic hypoperfusion.[9] Ahmad et al. found that aggressive diuretic strategies, observed WRF and increases in tubular injury biomarkers at 72 hours were not associated with adverse outcomes but rather with a paradoxical trend toward improved outcomes. These declines in estimated glomerular filtration rate (eGFR) likely represent clinically benign changes in filtration rather than a manifestation of tubular injury to the kidney.[10]

Data on urine output and characteristics (such as natriuresis) that are missing in Presume et al.'s study[5] could have shed more light on the pathophysiology underlying early WRF, revealing whether these patients might have had an inadequate response to diuretic therapy.[5] Similarly, data on weight loss and changes in natriuretic peptides, and even assessment of patients' symptomatic and hemodynamic status, would have brought more insight.

After discharge, prognosis is greatly influenced by prognosis-modifying therapy, especially in HF patients with reduced ejection fraction (HFrEF). In Presume et al.'s study, patients with HFrEF were well medicated at discharge, with 75.8% on angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, 72.7% on beta-blockers and 53.0% on mineralocorticoid receptor antagonists. But the fear of hyperkalemia or of further deterioration in renal function often makes physicians reluctant to initiate or to titrate agents acting on the renin-angiotensin-aldosterone system (RAAS) and the sympathetic system,[11] the main treatment for HFrEF, during hospitalization for HF. Therefore, HF patients with concomitant CKD are less likely to receive new guideline-recommended therapies. Nevertheless, in the majority of HF trials targeting the RAAS, benefits were observed regardless of the presence of CKD, even though patients with more severe CKD (SCr >2.5 mg/dl or eGFR <30 ml/min/1.73 m^2) were excluded. Furthermore, recent trials with sacubitril/valsartan and sodium/glucose cotransporter 2 (SGLT2) inhibitors, along with cardiovascular benefits, demonstrated improved renal outcomes, slowing the rate of decrease in eGFR.[6] It is important to remember that initiation of SGLT-2 inhibitors is associated with an initial transient and mild fall in eGFR over the first weeks. This initial mild drop in eGFR should not lead to premature discontinuation of SGLT-2 inhibitor therapy.[11]

Presume et al.'s study illustrates a latent concept that could be called the 'chronological phenotyping of WRF'. When dealing with an AHF episode, physicians should be looking further into the clock of kidney dysfunction.

Conflicts of interest

The author has no conflicts of interest to declare.

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