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WHAT'S NEW IN INTENSIVE CARE

Diuretics in cardiorenal syndrome: what's new?

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Introduction

The heart and kidneys are closely interrelated, from both a hemodynamic and neurohumoral perspective. Therefore, it should not be surprising that organ dysfunction in the one organ strongly impacts the other. Cardiorenal syndrome or worsening renal function during a cardiac insult or its treatment is therefore a frequently encountered scenario in clinical practice, with an incidence depending on the exact definition used. Different pathophysiological culprits may apply depending on the timeframe, i.e., acute (type 1) or chronic (type 2). In cardiorenal syndrome, diuretics are irreplaceable in terms of compensation for disturbed volume homeostasis. However, diuretic treatment, although frequently used, remains largely empirical, with little solid evidence currently available to guide decisions. Fortunately, a number of interesting developments may hold promise for a better future. In this short review we focus on three themes in the field of cardiorenal syndrome which have received attention in 2016: the concept of transient or pseudo-worsening renal function [1]; determinants of diuretic efficacy in heart failure (HF) [2]; new therapies on the horizon with possible nephroprotective effects [3].

Pseudo-worsening renal function versus diuretic efficacy

Glomerular filtration rate

It has become increasingly clear in recent years that pursuing a strategy of thorough decongestion and avoidance of persistent volume overload upon discharge after an episode of worsening HF is crucial to prevent early readmissions, even when coming at the cost of a drop in glomerular filtration rate (GFR), which is often a transient phenomenon [1, 2]. Diverse novel biomarkers slightly improve the detection of acute kidney injury and enhance risk stratification, but more importantly they show that in the context of HF most rises in serum creatinine level are not associated with structural damage to glomeruli or tubules; hence the term pseudo-worsening renal function [3]. Indeed, a rising serum creatinine level associated with successful decongestion correlates with better—not worse—outcome [1]. Importantly, this phenomenon has been studied specifically in patients with acute HF and does not necessarily apply to an intensive care environment. From a pathophysiological perspective, however, one might expect that a rising serum creatinine level due to transient hemodynamic changes rather than structural nephron damage as a result of direct exposure to toxins or prolonged hypoperfusion should not defer the clinician from pursuing early decongestion in the critically ill patient as this condition is associated with less mechanical ventilation and a lower risk for respiratory infections.

Tubular function

The kidneys' unique anatomy allows for a very high GFR—equal to 180 L per day—which is pivotal for the clearance of toxic metabolites and waste products, while at the same time minimizes losses of water, nutrients, essential electrolytes, and oligo-elements through a sophisticated tubular reabsorption system. As even patients with a severely reduced GFR produce substantial amounts of tubular fluid through ultrafiltration, volume homeostasis is primarily determined by this tubular system [4]. The responsiveness of the tubules to loop diuretics (i.e., loop diuretic efficacy defined as natriuresis/diuresis per dose administered) is a powerful predictor of clinical outcome in HF, irrespective of the underlying GFR (Table 1) [5, 6]. A logical but still unproven hypothesis is that therapeutic interventions improving diuretic

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efficacy may ultimately lead to better clinical outcome in HF. To assess this possibility, better insight into the phenomenon of diuretic efficacy is needed.

Determinants of diuretic efficacy

Neurohumoral blockers

An interesting finding was reported in 2016 by Kula et al. who studied 656 consecutive patients with acute HF and volume overload [7]. The authors found that up-titration of guideline-recommended neurohumoral blockers to hospitalized patients, although associated with a modest reduction in blood pressure and lower GFR, was associated with significantly improved diuretic efficacy and decongestion. While the study was observational with the inherent potential of indication bias, the results provide reassurance that the guideline-recommended titration of chronic oral medication during an acute HF hospitalization is not antagonistic to the short-term goal of decongestion, yet may be crucial to improve clinical outcome by mediating diuretic efficacy.

Use of urinary electrolyte panels

Based on the results of their study involving 50 HF patients with marked volume overload, Testani et al. reported that a poor natriuretic response can be predicted with excellent accuracy soon after diuretic administration using spot urine sampling [8]. High urinary sodium concentration early after loop diuretic administration seems to hallmark favorable diuretic efficacy, with estimated total natriuresis approximated by the following formula: $0.15 \times \text{GFR} \times [\text{creatinine}]_{\text{serum}} \times [\text{Na}]_{\text{urine}}$ over $[\text{creatinine}]_{\text{urine}}$, with adjustments for body surface area. This may indicate that looking more closely at urinary electrolyte panels may offer valuable information to improve the management of cardiorenal syndrome and possibly guide diuretic administration.

Hypochloremia and diuretic resistance

The strong association between hypochloremia, diuretic resistance, and poor clinical outcome in HF has been increasingly acknowledged [9–11]. In the Placebo-controlled Randomized Study of the Selective A1 antagonist Rolofylline for Patients Hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) trial ($n = 2033$), hypochloremia of <96 mmol/L was associated with high bicarbonate levels, poor diuretic efficacy, less hemoconcentration, and worsening HF [10]. Newly developed hypochloremia during decongestive treatment was common and associated with declining GFR and increased blood urea nitrogen. Hypochloremia that resolved was not associated with mortality, but new or persistent hypochloremia was (hazard ratio 3.11, 95% confidence interval 2.17–4.46). Results from the Renal Optimization Strategies Evaluation in Acute Heart Failure (ROSE AHF) corroborate these findings, yet show that the absolute change in serum chloride levels is a poor surrogate for clinical outcome [11]. While demonstration of an association not necessarily implies a causal relationship, it should be mentioned that chloride-sensing in the macula densa is determining the tubulo-glomerular feedback, which governs the plasma volume set-point and renin release to activate the renin–angiotensin–aldosterone system [4]. Intriguingly, diuretics working in the proximal renal tubules (i.e.,

Table 1 Relationship between diuretic efficacy and clinical outcome in heart failure

References	Metric	Findings in patients with low diuretic efficacy
Testani et al. [5]	Net fluid loss[a]	Higher all-cause mortality (after correction for diuretic dose, fluid output and baseline characteristics)
Valente et al. [16]	Weight loss[a]	More HF readmissions after 60 days Increased death, HF, or renal related readmissions after 60 days Higher all-cause mortality after 180 days
Voors et al. [17]	Weight loss[a]	Increased death, HF, or renal related readmissions after 60 days Neutral effect on all-cause mortality after 180 days
Singh et al. [18]	Urinary sodium/furosemide concentration	Increased death, transplantation or readmission for HF (after correction for eGFR)
Ter Maaten et al. [19]	Weight loss[a] Urine output[a]	Increased death or HF readmissions after 30 days
Verbrugge et al. [12]	Natriuresis[a]	Increased death or HF readmission (after correction for eGFR)
Kumar et al. [20]	Fractional sodium excretion	Higher all-cause mortality after 30 days
Aronson et al. [21]	Net fluid loss[a] Urine output[a]	Higher all-cause mortality after 6 months

HF, Heart failure; eGFR, estimated glomerular filtration rate

[a] Per 40 mg of intravenous furosemide-equivalent dose

acetazolamide) may prevent bicarbonate accumulation and hypochloremia to improve diuretic efficacy by offering more chloride to the macula densa [12].

New therapies with potentially nephroprotective effects

Three novel therapies, all with the potential to play a future role in the treatment of HF, may be particularly interesting to study in the context of cardiorenal syndrome because they may exhibit nephroprotective effects. Serelaxin, a recombinant version of human relaxin-2, decreases systemic vascular resistance and increases renal blood flow, thereby improving symptoms and possibly alleviating structural nephron damage in acute HF, yet without a significant effect on diuretic response [13]. Phase III studies powered for clinical endpoint evaluation with serelaxin in acute HF are currently underway. Further, combined therapy with the neprilysin inhibitor/angiotensin receptor blocker sacubitril/valsartan promotes the endogenous natriuretic peptide system, which may improve diuretic efficacy and is associated with improved mortality and less worsening renal function in patients with chronic HF [14]. Finally, the sodium–glucose transporter-2 empagliflozin has been shown to slow GFR deterioration and reduce the need for dialysis as well as strikingly reduce HF hospitalizations by one-third in a population with diabetes and established cardiovascular disease [15]. While it is too soon to recommend the use of any of those therapies in cardiorenal syndrome yet, for sure they will be the topic of future research.

Clinical implications

How should this recent evidence influence clinical practice? First, it should be appreciated that biomarkers for glomerular function do not necessarily reflect the kidneys' ability to govern volume homeostasis. Thus, in the setting of clear volume overload, a rising serum creatinine level should not be the reason underlying the decision of the critical care physician to not pursue decongestion with diuretics. Similarly, neurohumoral blockers such as angiotensin-converting enzyme inhibitors should not be withheld in HF patients because of transient changes in GFR if urine output is preserved. Secondly, high urinary sodium concentration after diuretic administration indicates good diuretic efficacy and should probably be more routinely assessed. In contrast, a low serum chloride level defines a population that is relatively diuretic resistant and for whom the optimal decongestive treatment remains unsure. Finally, mechanistic studies should be performed to determine the potential value of serelaxin, sacubitril/valsartan, and sodium–glucose transporter-2 inhibitors in the management of cardiorenal syndrome.

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