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WHAT'S NEW IN INTENSIVE CARE

What's new in cardiorenal syndrome?

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Introduction

Cardiorenal syndrome (CRS) is a bidirectional disorder in which heart and kidney may induce or perpetuate disease in the other organ [1, 2]. Five subtypes reflecting the primary dysfunction and its chronicity have been described. This "what's new" paper will focus on CRS type 1 in which acute heart failure (AHF) (mostly in the setting of cardiogenic shock or acute decompensated heart failure) induces renal dysfunction and/or injury. CRS type 1 is common, may affect 25–33% of patients with AHF, and is associated with a grim prognosis [2, 3].

Definition and pathophysiology

The pathophysiological mechanisms underlying CRS type 1 include renal hypoperfusion due to hypotension and low cardiac output, renal congestion, maladaptive activation of the renin–angiotensin–aldosterone and the sympathetic nervous system, and inflammation [1, 2]. Recent literature has shifted from low cardiac output to venous congestion (causing increased renal backpressure and compartment syndrome) as the major pathophysiological mechanism [1, 4].

Renal congestion remains difficult to identify. Hence, although unadjusted risk of AKI increases steadily with increasing central venous pressure, this relationship is linear without clear threshold [5]. Besides hemodynamic parameters of congestion, novel imaging techniques such as renal vein Doppler patterns might be useful [6]. ST2, an interleukin-1 (IL-1) receptor family member, is a new biomarker of congestion, less affected by kidney function than NT-ProBNP and may add to its diagnostic and prognostic information [7].

An important impediment that hampers the interpretation of the literature on type 1 CRS is the absence of a consensus definition. In the cardiologic literature, it is mostly described as worsening renal function (WRF) during hospitalization and treatment of AHF. The most commonly used criterion for WRF is an increase of serum creatinine of at least 0.3 mg/dL or at least 25% over the first 5 days of hospitalization which differs from the current KDIGO definition for acute kidney injury (AKI) [1]. In addition, the definition of WRF does not include AKI on admission, which is associated with mortality and cardiovascular events [8].

Significance of worsening renal function and role of biomarkers

Since congestion is the major pathophysiological mechanism of CRS type 1, a beneficial effect of diuretics is to be expected. Benefits and feasibility of decongestion is, however, heterogeneous. In the same line, impact of decongestion on outcome is inconstant. A post hoc analysis of the DOSE trial, evaluating diuretic dosing in AHF, showed that improved renal function during decongestion therapy, rather than stable or WRF, was associated with worse outcome [9]. Similarly, others studies have shown that in the situation of successful decongestion with hemoconcentration (a surrogate of intravascular volume status), WRF has less prognostic impact than in patients with persistent congestion and absence of hemoconcentration [10]. This apparently surprising finding is partly due to confounders in serum creatinine evaluation. In the context of decongestion, serum creatinine elevation may result from mechanisms independent from decreased glomerular filtration rate (GFR) such as hemoconcentration (reducing the distribution volume of creatinine) (Fig. 1). This harmless and mostly transient renal dysfunction in the context of clinical improvement has also been called pseudo-WRF. The concept of pseudo-WRF may explain why biomarkers of tubular injury were found to be poor predictors of WRF in the setting of AHF, previous studies being liable to mix true AKI and pseudo-WRF [11, 12]. A recent study showed

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that during aggressive decongestion increased serum creatinine occurred in 22% of the AHF patients without increase in damage markers, further suggesting a potentially high proportion of pseudo-WRF or transient AKI due to excessive decongestion [11]. However, in the setting of WRF, damage markers may probably help in predicting outcome of renal dysfunction (Fig. 1) [13, 14].

Treatment of CRS type 1

The search for effective treatment in CRS type 1 has been largely unsuccessful and current guidelines for AHF do not provide specific guidance for this subgroup [15]. Effective decongestion with diuretics and vasodilators remains the mainstay of the initial treatment of AHF. Signs of reduced cardiac output should trigger inotropes. Observational data suggest that vasodilators and inotropes provide similar hemodynamic decongestion and have no short-term (24 h) effect on renal function [16]. Preliminary data suggest direct renal benefit for levosimendan in heart failure, but this requires confirmation in a large randomized controlled trial (RCT) [17].

Intensifying standard therapy targeting urine output may increase the success rate without deleterious effect on kidney function [18]. However, determining the efficacy of decongestion may be difficult and pseudo-WRF is likely to trigger potentially inappropriate discontinuation of treatment. Promising parameters that may guide decongestion therapy are numerous but poorly studied and include kidney damage markers [13], clinical and biochemical markers of congestion, such as BNP or the previously mentioned ST-2 [7], clinical signs of hypoperfusion, urine output or diuretic responsiveness, weight loss, and hemoconcentration. In this line, decongestion along with real-time monitoring of glomerular filtration, not yet available in clinical practice, might avoid unnecessary and potentially deleterious therapeutic changes. Although multimodal evaluation using these parameters seems promising in optimizing decongestive therapy, prospective validation of this concept is lacking [10].

In case of diuretic resistance ultrafiltration should be considered, although the most recent trial failed to show renal benefit and even suggested harm in comparison with standard treatment.

New treatments targeting congestion and neurohormonal activation in AHF such as nesiritide, tolvaptan, rolofylline, ularitide, and serelaxin did not pass the test of the large RCT (references in supplement). Valsartan/sacubitril, a combination of an angiotensin receptor blocker (ARB) and a neprilysin inhibitor, has shown decreased mortality and improved kidney outcomes compared with

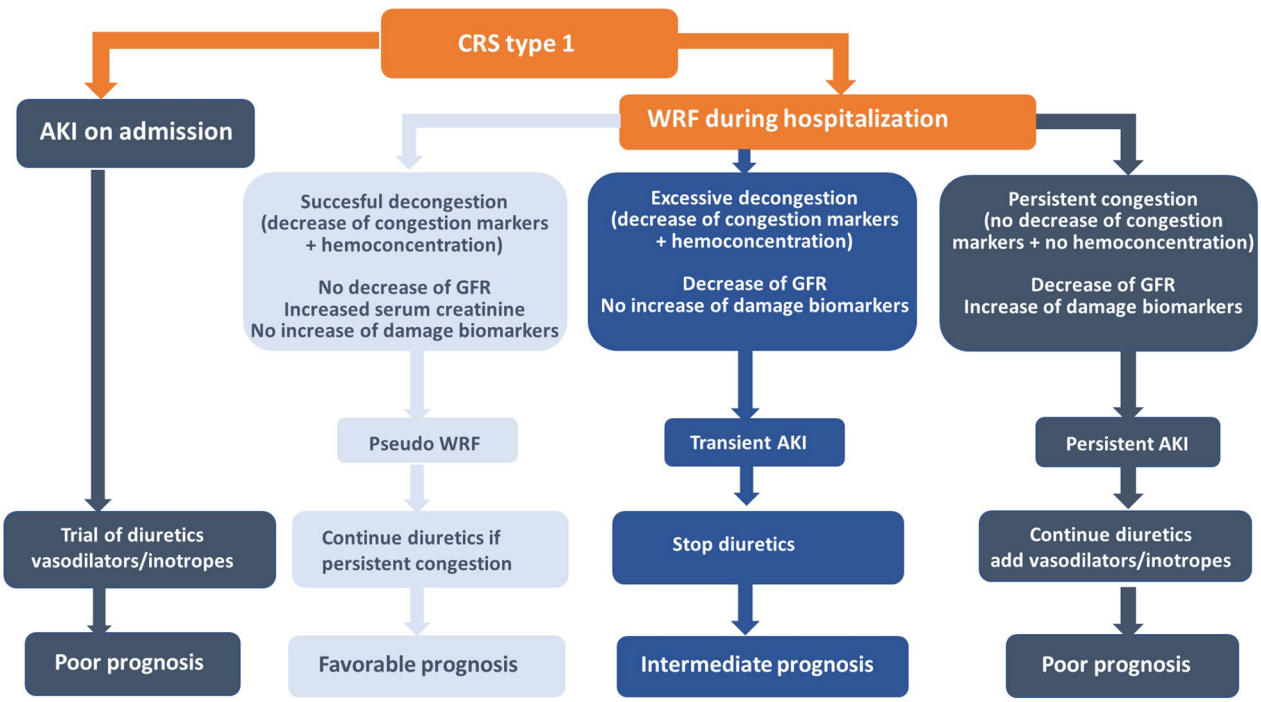

Fig. 1 Pathophysiology of different presentations of CRS type 1 with suggested treatment and prognosis. AKI on admission has poor prognosis—the prognosis of WRF during hospitalization depends on whether it concurs with successful, excessive, or unsuccessful decongestion. Treatment suggestions are provided by authors on the basis of currently perceived pathophysiology. Validity of this theoretical frame requires validation by prospective studies. AKI acute kidney injury, CRS cardiorenal syndrome, GFR glomerular filtration rate, WRF worsening of renal function

enalapril and is likely to revolutionize the treatment of chronic heart failure with reduced ejection fraction [19]. Its place in the management of AHF is, however, unclear, 20% of the patients in the run-in phase being unable to tolerate the drug because of hypotension.

In the absence of a clear panacea for the management of CRS type 1, timely introduction and optimization of treatments according to recent guidelines remains the best available option [15]. Future developments should include uniform criteria for the diagnosis of CRS, along with implementation and validation of strategies based on reliable parameters allowing distinction of pseudo-WRF from renal dysfunction.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-018-5190-0) contains supplementary material, which is available to authorized users.

Abbreviations
AHF: Acute heart failure; AKI: Acute kidney injury; CRS: Cardiorenal syndrome; GFR: Glomerular filtration rate; WRF: Worsening renal function.

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Compliance with ethical standards

Conflicts of interest
None to declare.

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