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Commentary

Ultrafiltration in decompensated heart failure: Is time to look forward?

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Heart failure (HF) is a chronic condition resulting in more than 1 million hospitalizations annually in both the United States and Europe [1]. Because the natural history of HF is characterised by disease progression and episodes of acute decompensation most of HF patients are admitted for decompensated chronic HF [1]. The vast majority of signs and symptoms of patients presenting with decompensated HF are caused by pulmonary and systemic congestion [1], the wet haemodynamic profile which reflects increased cardiac filling.

One of the main target for symptoms relief is to effectively resolve fluid overload. While diuretics are the cornerstone of therapy, kidney dysfunction and loop diuretics resistance often characterize the clinical course of patients with multiple episode of HF decompensation, and this may challenge the effective achievement of euvolemia.

Extracorporeal ultrafiltration (UF), consisting of the production of plasma water from whole blood across a semipermeable membrane in response to a transmembrane pressure gradient [2], is a further therapeutic option for the decongestion of these patients. UF may have some potential advantages as the reduction of diuretic-induced neurohormonal activation, and a more controlled rate (and amount) of fluid removal. Moreover, by removing isotonic plasma, an higher rate of sodium removal is expected compared with diuretic agents where hypotonic urine is excreted [2]. However, despite this strategy is clinically appealing, controversial findings on the clinical benefit of UF in the setting of decompensated HF have been reported [3–5].

Ullah et al. [6] presented a meta-analysis which faces some important clinical aspect related to the efficacy and safety of the available options for obtaining fluid removal in patients with acute decompensated HF. Analysing clinical trials which compared the use of UF versus diuretic approach in acute decompensated HF the Authors found that, at a median follow-up of 90 days, UF does not provide significant benefits in reducing the risk of a composite of all-cause mortality and all-cause re-hospitalizations (OR 0.71, 95% CI 0.47–1.07), all-cause mortality (OR 1.08, 95% CI 0.77–1.52) and heart failure-related re-hospitalization (OR 0.47, 95% CI 0.21–1.02). These findings are in line with the observed similar efficacy between the two groups in terms of mean difference in the fluid loss, weight changes, and length of hospital stay. UF appeared to be safe, the in-hospital risk for hypotension and post-therapy creatinine rise (>0.3 mg/dL) was not significantly different between the UF and diuretics arms. However the Authors did not report the rate of catheter-related complications as potential bleeding and infections which may occur in UF. Considering the integration of multiple findings and the global estimated effects, this study provide evidence for a similar effect of UF and pharmacologic treatment on short-term hard endpoints. Therefore, considering cost and healthcare staff utilization for UF, it cannot be recommended as a first-line therapy in severe decompensated HF and should not be employed indiscriminately in all congested patients.

Some previous discrepant results on the impact of UF in HF patients may be related to the differences in study design and to the different approach to UF in each study. For example in most studies diuretic therapy was stopped during UF whereas in others diuretic agent therapy was continued [7]. Some studies initiated UF earlier [3,4] compared to others which initiated UF after worsened renal function [5], but no study focused on comparison of early vs. late UF initiation. In addition, fluid removal rates were non-homogeneous and the ideal rate of fluid removal is still uncertain. Finally, clinical severity of decompensated HF and short term outcomes are often determined by the complex interplay between precipitant causes, the underlying cardiac disease, and the patient's comorbidities, factors that even randomization cannot surely balance in small randomized trials. Therefore which subset of HF patients might benefit the most from UF, and when and how UF could have the best clinical effect remains not fully elucidated.

Decompensated HF is a complex entity and multiple strategies usually need to be implemented simultaneously. Tailored administration of stepped pharmacological therapy including adjustable doses of intravenous loop diuretic agents, vasodilators and inotropes based on the hemodynamic profile is fundamental, together with an early assessment of diuretic response, renal status and subsequent hemodynamic adaptation. Net fluid output and changes in body weight are frequently used to assess the adequacy of diuretic therapy, and the measurement of

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urinary sodium content has been recently proposed [8]. Algorithmic approaches on diuretic dosing may be difficult to be applied in clinical practice considering the variable degree of volume overload and the influence of body weight, kidney function and of previous treatments on diuretic response. However, some standardised approach on the use of diuretics in HF with congestion is recommended from the HF Association of the European Society of Cardiology [9]. An impaired sensitivity to diuretics, however, remain a commonly encountered clinical scenario and may limit the achievement of proper and rapid decongestion in clinical practice [10]. The pathophysiology of diuretic resistance is often multi-factorial [11] and may result by activation of neuro-hormonal systems, by prolonged exposure to loop diuretics leading to nephron remodeling and compensatory increasing of sodium reabsorption but also by intravascular fluid depletion due to slow plasma refilling. Patients with diuretic resistance has lower blood pressure, more comorbidities, lower estimated glomerular filtration rate (eGFR) and sodium [10]. After non-response to IV loop diuretics, sequential nephron blockade with thiazides or thiazide-like diuretics is recommended [9]. Hemodynamic profile and renal function are strictly related; indeed glomerular filtration rate is dependent by arterial and venous renal pressures gradient which must remain sufficiently large for optimal filtration. High renal venous pressure due to elevated central venous pressure, one of the hallmarks of congestion, may reduce pressure gradient across the kidney with consequent decline of glomerular filtration rate. In this setting a faster strategy compared to diuretic, to decrease central venous pressure with a rapid but controlled fluid removal, could be useful for improving renal function and reducing diuretic resistance. This could be also applied to those hypotensive patients where forcing diuresis using prolonged inotropes and vasopressors administration could expose them to drugs-related adverse events.

An unresolved challenge is the ability to discern whether increase in serum creatinine represents a desired effects of hemoconcentration or undesired deterioration of renal function. However worsening renal function (WRF) (defined as an increase in creatinine by more than 0.3 mg/dL) that may occur during aggressive decongestion and escalation of HF therapy is not universally associated with adverse outcomes [12] but may have an additive prognostic value when it occurs in patients with persistent signs of congestion [13]. Considering that residual congestion is a strong predictor of poor outcome and readmission, this may suggest that decongestion should be pursued even at the risk of WRF. HF patients with poor response to intravenous diuretic therapy and persistent fluid overload despite the use of high-dose and combination of diuretic agents could be considered eligible for UF, and especially those with low urinary sodium concentration. Therefore in the armamentarium against fluid overload, UF may be reserved as a bail-out therapy to relieve congestion in patients truly refractory to diuretics. A multidisciplinary (cardio-renal) team approach is important for individualized patient-centered care and to meet the needs of HF patients with high complexity of care.

Future research should investigate whether the increasing implementation [14] of angiotensin receptor-neprilysin inhibitor (ARNI) which may modify neurohormonal maladaptation, and the introduction of sodium-glucose cotransporter-2 (SGLT2) Inhibitors with their effects on diuresis and natriuresis [15], may improve the treatment of congestion and diuretic resistance in patient with HF.

The results of the metanalysis by Ullah et al. [6] should stimulate new research for searching new effective and safe pharmacologic or mechanical method to treat congestion, and to optimally evaluate full decongestion. Precision medicine continues to evolve and also the "precision" of fluid removal should be pursued in the individual patients for effectively tackling congestion in acute decompensated HF. There are a lot of challenges ahead but looking forward may give us a purpose, which is by itself, motivating.

Declaration of Competing Interest

Nothing to declare.

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