Extracorporeal Ultrafiltration for Acute Heart Failure: Lost Battle or Lasting Opportunity?

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Key Words

Cardiorenal syndrome · Congestion · Diuretics · Heart failure · Ultrafiltration

Abstract

The negative prognostic impact of congestion and worsening renal function in patients with decompensated heart failure (HF) has been widely recognized. As diuretics are thought to provide suboptimal results and are associated with a number of adverse effects, a number of diuretic-sparing therapeutic strategies have been explored. Extracorporeal ultrafiltration (UF) represents an intriguing option that presumably lacks many of the untoward effects of diuretic-based regimens while portending several advantages. However, conflicting data have recently emerged in relation to some of its previously proposed beneficial effects possibly due to counterbalance of the underexplored mechanisms. Herein, the existing literature on the role of UF therapy for management of acute decompensated HF is briefly reviewed with special emphasis on its impact on surrogates of efficacy and safety such as excess fluid removal and renal function. A number of topics relevant to cardiorenal syndrome such as congestion and sodium removal are also discussed.

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Background

Heart failure (HF) is a major public health problem with a prevalence of more than 5.8 million in the United States and more than 23 million worldwide [1]. Acute decompensated HF (ADHF), defined as ‘gradual or rapid change in HF signs and symptoms resulting in a need for urgent therapy’, accounts for more than 1 million hospitalizations in the United States annually, with costs reaching \$30.7 billion in 2012 [2, 3]. In spite of the major advances in chronic HF management, the morbidity and mortality of ADHF remain high, resulting in the significant impairment of the quality of life of the patients and high health care cost burden. Congestion is the primary reason for hospitalization in a great majority of patients with ADHF [4]. It has been shown that right ventricular systolic pressure and pulmonary artery diastolic pressure increase significantly several days prior to admission for ADHF suggesting that subclinical volume overload precedes clinical congestion [5]. Moreover, adequate decongestion determined by either invasive or noninvasive parameters has been linked with improved outcomes in these patients [6]. Currently available therapeutic regimens for decongestion, which heavily rely on diuretic use, are associated with a number of shortcomings (table 1). Diuretics are known to cause electrolyte abnormalities, deteriora-

Table 1. Potential shortcomings of diuretic use in the treatment of HF

Direct activation of RAAS
Deterioration in renal function
Electrolyte abnormalities (e.g. hypokalemia and hypomagnesemia)
Suboptimal natriuresis (production of hypotonic urine)
Development of diuretic resistance
Unpredictability of the therapeutic response
Lack of clarity on the practical aspects of use (e.g. optimal dosing strategy)
Non-renal adverse effects (e.g. ototoxicity and hypersensitivity)
RAAS = Renin-angiotensin-aldosterone system. Adopted with permission from Kazory [47].

Table 2. Proposed advantages of UF for HF

Reduction in renal venous congestion and improvement in renal hemodynamics
Rapid and adjustable removal of fluid and improvement in symptoms of congestion
Higher mass clearance of sodium
Decreased risk of electrolyte abnormalities (e.g. hypokalemia)
Lack of neurohormonal activation (SNS, RAAS, and AVP)
Sustainability of the beneficial effects (e.g. impact on neurohormonal axis)
Improvement in diuretic resistance, natriuresis, and urine output
Decreased rate of HF-related re-hospitalization
Decreased hospital length of stay
Availability of dedicated UF devices that are portable, user friendly, with minimal extracorporeal volume (33 ml), and have the ability of functioning with low blood flow rates (10–40 ml/min)
SNS = Sympathetic nervous system; RAAS = renin-angiotensin-aldosterone system; AVP = arginine vasopressin. Adopted with permission from Kazory [47].

tion of renal function, neurohormonal activation, and non-renal adverse effects. Suboptimal diuresis, diuretic resistance, and unpredictability of the therapeutic response pose additional challenges for the use of these medications in the setting of ADHF, which in turn lead to worsening or lingering congestion. In a study of more than 50,000 patients, it was revealed that nearly half of the patients admitted for ADHF and congestion do not experience clinically relevant reduction in their weight during hospitalization [7]. Moreover, observational data are suggestive of an association between high-dose loop diuretic therapy and ad-

verse outcomes. However, since patients with severe congestion are the ones who require higher doses of diuretics, it is not yet clear whether the diuretic dose is indeed a marker of severity of the disease or a cause for adverse outcomes [8, 9]. Unfortunately, the newer pharmacologic agents such as endothelin receptor antagonists, vasopressin receptor antagonists, and adenosine-A1 receptor antagonists have failed to prove their role as safe and effective alternatives to conventional therapies. Consequently, there has been a renewed interest in exploring non-pharmacologic therapies like mechanical extraction of the excess fluid (i.e. ultrafiltration (UF)) as an effective alternative to the conventional approaches aimed at decongestion in ADHF. UF therapy has several proposed advantages including relatively rapid, predictable, and adjustable fluid removal, activation of the renin-angiotensin-aldosterone system to a lower degree compared with diuretics, and more effective sodium removal. The proposed benefits of UF therapy are summarized in table 2.

Efficacy and Safety

Because congestion is the major cause for hospitalization in the majority of patients with ADHF and portends poor outcomes, the efficacy of the therapeutic options is mainly determined by how well they can decongest the patients [10, 11]. Two primary surrogates commonly used for evaluation and monitoring of decongestion are the ability of a therapeutic modality to remove excess fluid and the associated weight loss. Safety of the ADHF therapy is of utmost importance and commonly includes various markers and definitions of impairment in renal function. Renal dysfunction is one of the strongest predictors of poor clinical outcomes in this setting and the risk of mortality in patients with reduced glomerular filtration rate is reported to be more than double that of those without renal impairment [12]. It is also shown that worsening renal function (WRF) during the treatment of ADHF could be associated with poor outcomes irrespective of the baseline kidney function [13].

Emerging data suggest that congestion has a bidirectional relationship with both the kidney and the heart in the setting of cardiorenal syndrome, where acute decompensation of the heart contributes to deterioration in renal function through a number of mechanisms leading to low forward flow and high backward pressure in the kidney (fig. 1). Interestingly, congestion has also been shown to affect the impact of renal dysfunction on clinical outcomes and can be considered a link between the surrogates of ef-

Fig. 1. Bi-directional pathways linking HF, renal dysfunction, and congestion in cardiorenal syndrome. Decompensation of HF can lead to the deterioration in renal function via exacerbated neurohormonal activity (i.e. low forward flow) or through fluid overload and

renal venous congestion (i.e. high backward pressure). UF could counter these maladaptive interactions mainly by correcting congestion. LVEDP = Left ventricular end-diastolic pressure; LVF = left ventricular function. Adopted with permission from [48].

efficacy and safety of therapies for ADHF. Indeed, an increase in serum creatinine that parallels fluid removal and weight loss is not associated with poor outcomes [14]. The complex interactions between congestion and other pathophysiologic mechanisms involved in HF and cardiorenal syndrome are beyond simple impact on hemodynamics, and are indeed reminiscent of the pro-inflammatory role of fluid overload in the setting of acute kidney injury [15–19]. Therefore, in order to fully examine the role of various therapeutic options for ADHF and compare their impact, these interactions need to be taken into account.

In addition to WRF, outcome measures such as hospital readmission rates and prolonged hospital stays contribute to low quality of life of HF patients and high health care cost burden. The mortality rate of ADHF also remains significantly high. In a study that included Medicare beneficiaries hospitalized between 1998 and 2008 with a principal discharge diagnosis code for HF in United States and Puerto Rico, the risk-adjusted 1 year mortality was close to 30% [20].

Clinical Studies on UF

Several clinical studies have studied the role of UF in the management of patients with ADHF after it was first proposed for this indication in 1970s by Silverstein et al. [21]. The initial studies focused on the mechanistic aspects of UF and its effects on various physiologic, neurohumoral, and hemodynamic parameters [22–24]. Marketing of the newer user-friendly portable devices that are dedicated to UF for HF, with the ability of using peripheral or midline venous catheters, low blood flow rate, and low extracorporeal blood volume generated further interest in this modality. Later, more clinical studies were designed to assess the reproducibility of preliminary findings and to provide answer to practical questions such as indications, optimal timing, efficacy, and untoward effects. In this study, we briefly review the findings of the most important studies in this field and provide explanations for some of the results. As mentioned earlier, fluid removal and weight change have commonly

been used to define the efficacy of UF therapy, while impact on renal function in general is considered a measure of safety. A number of secondary endpoints such as HF-related rehospitalization and length of hospital stay have also been evaluated in the UF studies. Selected studies exploring the role of UF therapy in the management of ADHF have been summarized in table 3.

Decongestion

Until 2005, although several studies had already reported high efficacy of UF therapy in terms of decongestion, they included a small number of patients or lacked an appropriately matched control group. The relief for acutely fluid-overloaded patients with decompensated congestive heart failure trial randomized 40 ADHF patients with fluid overload to either receive a single 8 h UF session in addition to usual care, or usual care alone [25]. Patients in the UF group had significantly greater fluid removal (4,650 and 2,838 ml in the UF and usual care groups respectively, $p = 0.001$). After 48 h, fluid removal was 8,415 and 5,375 ml in the UF and usual care groups respectively ($p = 0.012$). Weight loss after 24 h, the primary end point, was higher in the UF group but failed to reach statistical significance (2.5 vs. 1.86 kg in the UF and usual care groups respectively, $p = 0.240$). Compared to usual care, UF was not associated with significant changes in heart rate, blood pressure, or electrolytes. This study showed the tendency of UF therapy for better decongestion and set the stage for larger trials.

UF versus intravenous diuretics for patients hospitalized for ADHF (UNLOAD) trial is a large multicenter randomized controlled trial of 200 patients that compared the effect of UF ($n = 100$) and standard therapy ($n = 100$) in patients admitted with ADHF and hypervolemia [26]. In this study, patients with a serum creatinine level of greater than 3 mg/dl were excluded. Along with 2 liters/day fluid restriction, all patients received low-sodium (2 g/day) diet during admission. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers were continued throughout the study as tolerated. In the UF arm, during the first 48 h of enrollment, hypervolemia was treated exclusively with UF and intravenous diuretics were prohibited. The investigators reported that the net fluid loss after 48 h was greater in the UF group than in the standard-care group (4.6 ± 2.6 vs. 3.3 ± 2.6 liters; $p = 0.001$). Weight loss was also greater in the UF group than in the standard-care group ($5.0 \pm$

3.1 vs. 3.1 ± 3.5 kg; $p = 0.001$). In both arms, a significant correlation existed between the 48-hour weight and fluid loss ($r = -0.60$ and -0.40 , respectively, $p = 0.001$). Interestingly, despite more significant decongestion, dyspnea scores were found to be similar in both therapy arms. It has been suggested that the greater efficacy of UF therapy in excess fluid removal and decongestion is associated with improvement in hemodynamic status without exacerbation of neurohormonal activity. In a randomized controlled trial on 30 patients with ADHF, Giglioli et al. [29] used Pressure Recording Analytical Method to continuously monitor the cardiovascular impact of decongestion before, during, at the end of treatment, and 36 h after completing therapy. Compared to diuretics, the UF group showed a significant improvement in several hemodynamic parameters including stroke volume index ($114.0 \pm 11.7\%$; $p < 0.001$) and cardiac index ($123.0 \pm 20.8\%$; $p < 0.001$), and a significant reduction in systemic vascular resistance 36 h after the treatment ($88.0 \pm 10.9\%$; $p < 0.001$). Patients treated with UF also showed a significant decrease in serum aldosterone (0.24 ± 0.25 vs. 0.86 ± 1.04 nmol/l; $p < 0.001$) and N-terminal pro B-type natriuretic peptide levels ($2,823 \pm 2,474$ vs. $5,063 \pm 3,811$ ng/l; $p < 0.001$) compared with the diuretic group.

Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) trial is the most recent multicenter randomized study that was performed a few years later. In this trial, 224 patients with ADHF were randomized to either adjustable UF ($n = 110$) or stepped pharmacologic therapy (PT) that included loop diuretics ($n = 114$) [35]. Similar to UNLOAD trial, patients with renal insufficiency with a serum creatinine ≥ 3.0 mg/dl were excluded. Both arms were placed on daily fluid and sodium restriction of 1.5 liters and 1.5 g/day respectively and continued on guideline-directed medical therapy for HF except that diuretics were withheld in the UF arm. The average duration of the UF was 80 ± 53 h with an average rate of 138 ± 47 ml/h. During the hospital stay, the UF group had greater total amount of fluid removed (18.7 vs. 14.0 liters; $p = 0.015$) and the net fluid loss (12.9 vs. 8.9 liters; $p = 0.006$) was compared to the diuretic group. However, there was no statistically significant difference between the 2 groups in terms of weight loss at 72 h after randomization (10.7 ± 7.2 vs. 10.3 ± 9.2 kg; $p = 0.343$). It is of note that the AVOID-HF trial was designed to recruit 880 patients but had to be terminated earlier due to slower than expected recruitment process. In general, most studies of UF have shown the higher efficacy of this modality in removal of excess fluid and greater weight loss compared to conventional medical therapy.

Table 3. Selected trials of UF in HF

Study	Design	Total, n	Efficacy	Safety
Bart et al. [25], 2005 (RAPID-CHF)	RCT (comparison of 20 patients with UC and 20 with UF therapy. Patients received a single, 8-hour course of UF and diuretics were held during that period)	40	Fluid removal: 4.6 liters in UF group at 24 h (vs. 2.8 liters in UC group) Weight loss: 2.5 kg in UF group at 24 h (vs. 1.8 liters in UC group)	Renal function: no significant difference between 2 groups at 48 h Rehospitalization: not available Median length of stay: 6 days in UF group vs. 5 days in UC Mortality: 1 death in UF group unrelated to the procedure
Costanzo et al. [26], 2007 (UNLOAD)	RCT, with control group of diuretic therapy	200	Fluid removal: 4.6 liters at 48 h (vs. 3.3) Weight loss: 5 kg at 48 h (vs. 3.1)	Renal function: no significant difference between 2 groups (but percentage of patients with >0.3 mg/dl rise in Cr non-significantly more in UF group) Rehospitalization: low in UF group (185 vs. 32%) Rehospitalization days: fewer in UF group (1.4 vs. 3.8) Mortality: non-significant
Jaski et al. [27], 2008	Retrospective, cohort study	100	Fluid removal: 7.1 liters (2 sessions) Weight loss: 7 kg from pre-UF to discharge (there was correlation between these 2 parameters)	Renal function: no significant change Rehospitalization: not applicable Length of stay: not applicable Mortality: UF not significantly associated with long-term mortality
Bartone et al. [28], 2008	Retrospective (comparison of 25 patients with UF therapy, 25 with UC and 25 with UC plus nesiritide (UN))	75	Fluid removal: mean UF 12.2 liters in 37.5 h Weight loss: greater in UF group (7.17 vs. 2.85 kg UC and 2.13 kg UN)	Renal function: significant increase in UF group (44 vs. 24% UC and 20% UN) Rehospitalization: fewer in UF group (16 vs. 24% in UC and 20% in UN) Median length of stay: 6 days for UF, 4 days UC, 6 days UN Mortality: not available
Giglioli et al. [29], 2011 (ULTRADISCO)	RCT, PT vs. UF, Hemodynamic monitoring	30	Fluid removal: 9.7 liters in UF group at 36 h (vs. 7.8 liters in PT) Weight loss: 5.4 kg in UF group vs. 5.8 kg in PT (but percent change more in UF group)	Renal function: no significant difference between 2 groups at 36 h Rehospitalization: not available Length of stay: not available Mortality: not available
Dev et al. [30], 2012	Retrospective, UF typically used after failure of medical therapy	72	Fluid removal: 11.3 liters by UF Weight loss: 9.7 kg (after UF)	Renal function: 43% patients experienced >20% decrease in GFR during UF therapy, 10% required dialysis Rehospitalization: not evaluated Median length of stay: 17 days Mortality: not evaluated
Patarroyo et al. [31], 2012	Retrospective, SCUF used after failure of medical therapy	63	Fluid removal: 5.8 liters (48 h) Weight loss: 6 kg after SCUF (48 h)	Renal function: significant deterioration in those who began UF >48 h after admission. Fifty-nine percent required dialysis Rehospitalization: not available Length of stay: not available Mortality: 30%
Bart et al. [32], 2012 (CARRESS-HF)	RCT, PT vs. UF	188	Fluid removal: 4.7 liters in UF vs. 3.80 (non-significant) Weight loss: 5.7 kg in UF vs. 5.5 (non-significant)	Renal function: serum Cr significantly increased after UF Rehospitalization: no significant difference Length of stay: not available Mortality: 60-day mortality 17% in UF group, 13% in PT (non-significant)

Table 3. (continued)

Study	Design	Total n	Efficacy	Safety
Jefferies et al. [33], 2013	Prospective cohort study (comparison between HFLEF and HFPEF)	184	Fluid removal: 11.1 liters in HFLEF vs. 10.6 liters in HFPEF based on initial rate Weight loss: 7.56 kg in HFLEF vs. 6.4 kg in HFPEF	Renal function: Cr significantly increased after UF in HFLEF and increased but non-significantly in HFPEF group Rehospitalization: not available Length of stay: 8 days in both groups Mortality: deaths 90-day post discharge greater in HFLEF (24.1 vs. 15.5%)
Marenzi et al. [34], 2014 (CUORE)	RCT with UF or PT as first-line	56	Fluid removal: mean of 4.25 liters/34 sessions Weight loss: 7.5 kg in UF vs. 7.9 kg in PT (non-significant)	Renal function: no significant difference between both groups at discharge Rehospitalization: lower in UF group Length of stay: not different between the groups Mortality: no significant difference between 2 groups but mortality was relatively high (30.44%)
Costanzo et al. [35], 2016 (AVOID-HF)	RCT of UF vs. PT	224	Fluid removal: 12.91 liters UF vs. 8.91 l PT (significant) Weight loss: 10.7 kg in UF vs. 10.3 kg in PT (non-significant)	Renal function: no significant difference between the groups Rehospitalization: significantly lower in UF group for HF events, no difference in all-cause Length of stay: no significant difference between the groups Mortality: no significant difference in 90-day mortality

RCT = Randomized controlled trial; Cr = creatinine; GFR = glomerular filtration rate; HFLEF = heart failure with low ejection fraction; HFPEF = heart failure with preserved ejection fraction; UC = usual care; UN = usual care + nesiritide; PT = pharmacologic therapy; SCUF = slow continuous ultrafiltration.

Renal Function

Since diuretics, the mainstay of therapy of ADHF, can result in the deterioration of renal function via a number of mechanisms, and renal venous congestion has been shown to be associated with renal dysfunction, it was hoped that UF therapy could lead to conservation of renal function by virtue of avoiding diuretic use while relieving high venous pressure in the kidney. However, most studies did not show significant differences in changes in serum creatinine levels between UF and medical management groups while some even showed worse renal outcomes with UF. In a randomized controlled trial with a limited number of patients that was a sub-study of UNLOAD trial, Rogers et al. [36] meticulously measured renal function and renal plasma flow of the patients who were admitted to the hospital for ADHF. They reported similar impact of diuretics and UF on the measured parameters. In the continuous ultrafiltration for congestive heart failure (the CUORE trial), 56 patients with ADHF were randomized to receive standard medical therapy (n = 29) or UF (n = 27) [34]. At 6-month follow-up, serum creatinine in medical therapy group was 2.3 ± 1.1 vs. 1.8 ± 0.6 mg/dl in the UF group (p = 0.69). In line with that finding, larger studies like UNLOAD and AVOID-HF also showed no significant difference between both groups in terms of changes in renal function [26, 35]. In contrast to most other studies, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial, that randomized 188 patients with ADHF and WRF to UF or a well-designed stepped PT found significant worsening of renal function in the UF group at 96 h manifested by an increase in blood urea nitrogen and creatinine concentration (12.54 ± 24.81 vs. 5.68 ± 18.29 mg/dl; p = 0.02 and $+0.23 \pm 0.70$ mg/dl vs. -0.04 ± 0.53 mg/dl; p = 0.003, respectively) [32]. Interestingly, this unexpected finding was despite similar weight loss for both groups. It has been argued that the rate of fluid removal (200 ml/h) in the CARRESS-HF trial was not customized to the clinical characteristics (e.g. blood pressure) or the needs (e.g. degree of volume overload) of the patients while the medical therapy arm received a protocol-driven regimen that was meticulously adjusted based on the clinical and biological parameters such as renal function and urine output. However, it seems unlikely that the difference in customization of the therapeutic interventions could fully explain the negative impact of UF that was found in this trial.

In a recent study by Vazir et al. [37], the hemodynamic changes that take place during UF therapy were moni-

tored and their impact on renal function was assessed. The investigators used serial measurement of central venous oxygen saturation (CVO2), a surrogate for cardiac output, in 20 UF treatments for 17 patients with ADHF and diuretic resistance. As the initial 2 l of fluid were removed, a rise in CVO2 and a fall in serum creatinine were observed. However, upon further fluid removal there was a fall in CVO2 which corresponded to WRF. These results suggest that changes in renal function could be related to transient changes in cardiac output that take place during UF and might remain unnoticed unless monitored carefully. The subclinical hemodynamic compromise is likely to result from imbalance between UF rate and the rate at which the intravascular volume can be refilled from the extravascular compartment. This study underscores the importance of customization of UF therapy. Larger studies are needed to confirm these findings.

Rehospitalization

HF has the highest rate of readmission among all medical conditions (i.e. 27% at 30 days) [38]. Frequent hospitalizations not only could affect the quality of life of the patients, they represent a substantial burden on healthcare expenditure [39]. Moreover, readmission rates for HF are increasingly regarded as a quality metric and are being used to define reimbursement rates and penalize underperforming facilities (i.e. readmission-based financial incentive/disincentive programs) [40]. In the field of UF, some of the studies have evaluated HF-related rehospitalization as a secondary endpoint. In general, they have found that UF use can be associated with lower incidence of readmission compared to medical therapy. For example, in the UNLOAD trial, the UF group had fewer patients rehospitalized for HF (16 of 89 (18%) vs. 28 of 87 (32%); $p = 0.037$), HF rehospitalization (0.22 ± 0.54 vs. 0.46 ± 0.76 ; $p = 0.022$), and rehospitalization days (1.4 ± 4.2 vs. 3.8 ± 8.5 ; $p = 0.022$) per patient at 90 days [26]. Similarly, in AVOID-HF trial, the UF arm had fewer days in the hospital due to HF readmissions (68 vs. 172 days; $p = 0.029$), lower rehospitalization rates due to a cardiovascular event (17 vs. 33 days; $p = 0.037$), fewer rehospitalization days due to a cardiovascular event (88 vs. 207 days; $p = 0.018$), and fewer patients rehospitalized for a cardiovascular event (15 vs. 27 days; $p = 0.042$) [35]. The key information on the major studies and their findings are summarized in table 3.

Adverse Events

Although aforementioned studies support the concept of using UF in the management of HF, the long-term outcome of this approach has not been explored extensively. While fluid removal is the primary goal of UF therapy, it can potentially be hazardous when done excessively. Aggressive fluid removal can lead to decreased effective blood volume, hypotension, renal hypoperfusion, renal azotemia, and possibly acute kidney injury necessitating renal replacement therapy. This often occurs from mismatch between UF rate and vascular refill. In fact, plasma refill rate can be used to guide the rate of volume extraction in patients with HF undergoing UF to avoid inadequate decongestion. Hemoconcentration, reflected by a rising hematocrit is an appropriate surrogate to indicate that the plasma refill rate has been exceeded by the rate of fluid extraction. It can be monitored continuously by using an in-line hematocrit sensor during UF therapy [41].

Like with any pumped blood technology, several other potential adverse events are of concern while using the UF machines. They include, but are not limited to air embolism, undetected disconnection of the blood lines leading to hemorrhage, blood leaks within the hemofilter, catheter infections, allergic reactions to the ethylene oxide sterilant used in some dialyzers and tubing sets. Though these complications are very rare, the nursing staff and any practitioner offering these treatments should be able to detect them early and prevent serious hazards.

Current evidence suggests that the rate of adverse events might be higher in patients receiving UF therapy compared to those managed conservatively. For example, in the AVOID-HF trial, a higher number of patients in the UF group experienced 'serious adverse events deemed to be related to the study therapy' such as gastrointestinal bleeding and hematuria (due to anticoagulation) compared with those in the diuretic arm (14.6 vs. 5.4%; $p = 0.03$). Also, more patients in that group experienced an 'adverse event of special interest', like symptomatic hypotension necessitating intervention, infections, or cardiac events (31 vs. 17%; $p = 0.02$) [35]. In line with the above findings, the CARRESS-HF trial also had more patients in the UF arm with serious adverse event, such as bleeding and catheter-related complications (72% for UF versus 57% for medical therapy; $p = 0.03$) [32]. The exact cause for these increased adverse effects remains elusive. It would be interesting to explore whether a number of fundamental changes in the practice of UF therapy such

as increasing the involvement of nephrologists in the delivery of UF therapy through collaborative programs, training of physicians and staff as part of a comprehensive HF service, routine use of UF profiling, and real-time monitoring of intravascular volume would have a beneficial impact.

Sodium Removal

Multiple mechanisms that are involved in the development of ADHF lead to sodium retention which in turn, results in extracellular fluid expansion, volume overload and congestion. Therefore, any therapeutic modality with greater sodium extraction is expected to be advantageous in this setting. The findings of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan trial support this assumption. This was a randomized multi-center trial that included 4,133 patients hospitalized with HF who were randomly assigned to receive oral tolvaptan (thereby, promoting 'sodium-free' water excretion) or placebo in addition to standard therapy. The composite of cardiovascular death or hospitalization for HF occurred in 42% of tolvaptan group and 40.2% placebo group patients (hazard ratio 1.04; 95% CI 0.95–1.14; $p = 0.55$). Secondary end points of cardiovascular mortality, cardiovascular death or hospitalization, and worsening HF were also not different [42].

The fluid extracted through convective forces, as in UF therapy, is isotonic and so it is reasonable to assume that it removes a significantly higher amount of sodium compared with conventional PT, which typically results in hypotonic urine. But this opinion remains unproven and largely underexplored. In a small randomized pilot trial of target weight-guided therapy for ADHF, Chung et al. [43] compared the amount of volumes and sodium removed in 16 hospitalized patients. Total volume removed in both UF and diuretic arms was similar (11 and 10.7 liters, respectively). Sodium concentration was 138 ± 6 mEq/l in the ultrafiltrate, 85 ± 73 mEq/l in the diuretic group's urine, and 26 ± 23 mEq/l in the UF group's urine. Given the relevant associated volumes, the total amount of sodium removed was similar for both therapies (1,168 in diuretic group vs. 1,216 in UF group). A recent study by Verbrugge et al. [44] provides a useful insight into urinary sodium composition. Sixty one patients with HF with reduced ejection fraction and worsening symptoms were treated with protocol-driven intravenous diuretic therapy until complete decongestion, assessed clinically and by echocardiography. Urinary sodium and chloride

excretion significantly decreased, even after correction for diuretic dose ($p = 0.040$ and $p = 0.004$, respectively), leading to decreasing urinary concentrations with progressive decongestion, while their urine volume remained stable.

So far, no study has explicitly addressed this urinary sodium variability in patients treated with UF. However, it is conceivable that a similar decline in urinary sodium would occur with progressive decongestion and correction of the underlying total body sodium excess. The mechanism by which UF addresses volume overload is by removing fluid from the venous pool leading to interstitial decongestion and progressive intravascular volume contraction. This concept is supported by a recent study by Mentz et al. [45] on patients with ADHF that assessed the relationship between markers of RAAS activation (plasma renin activity and aldosterone) from baseline to 72 and 96 h of decongestion strategy. It was shown that UF resulted in greater increase in plasma renin activity than intravenous diuretic therapy. This could lead to enhanced proximal tubular sodium reabsorption and lowered urinary sodium offsetting the advantageous sodium-rich fluid extraction by UF therapy [46]. Therefore, the concept of enhanced sodium removal by UF compared to diuretics remains an assumption that has not yet been fully explored.

Conclusion

In summary, UF therapy for ADHF has the advantage of more effective decongestion, appears to be associated with improved secondary outcomes in the short-term (weeks to months after therapy), and does not appear to have a major clinically relevant adverse impact on renal function if started early. However, the long-term effects of this costly therapeutic option and its impact on the mortality remain largely unknown. Moreover, there is a signal of harm in terms of therapy-related adverse events for UF, and its previously observed beneficial effects could possibly dissipate if it is performed after development of renal dysfunction and cardiorenal syndrome. Currently available data come from studies that have commonly included patients with systolic HF. Indeed, none of the randomized controlled trials so far has compared HF patients with reduced ejection fraction with those who present with preserved ejection fraction.

In spite of limitations of the current studies and also the recent negative trials, UF seems to be useful in se-

lected subset of patients who are fluid overloaded and experience diuretic resistance, those with a history of frequent HF readmissions and suboptimal decongestion, especially if applied early in the course of hospitalization. Therapy should be customized based on the clinical characteristics and fluid goal, and tailored to the needs of each patient. We opine that collaborative efforts between nephrology and cardiology expertise could prove beneficial in the practice of UF-based therapies for HF patients. In addition, future large-scale

studies are needed to address the current gaps in literature and to determine the particular subset of patients who would most benefit from this expensive and labor-intensive therapy.

Disclosure Statement

No specific financial support was obtained for preparation of this article. The author has no potential conflicts of interest to declare with respect to this paper.

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