Ultrafiltration in acute heart failure: Current knowledge and fields for further research

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Abstract

Heart failure is one of the leading causes of death in developed countries and remains a significant burden to the healthcare system. Fluid overload is a process responsible for the majority of the heart failure symptoms. Pharmacotherapy is a first-line treatment for this condition; however, due to the phenomenon of diuretic resistance, drug therapy can frequently be insufficient. Ultrafiltration is a promising but still understudied procedure that effectively targets the underlying pathophysiological mechanisms of congestion. The increased availability of simplified ultrafiltration devices, especially in intensive care units, prompted us to perform a current literature review on this treatment. In the present paper, we provide a concise review of the published trials on ultrafiltration, with a brief commentary on their conclusions and shortcomings. We also discuss the practical aspects of this treatment that remain unclear, such as the accurate selection of patients, choosing a suitable protocol for ultrafiltration, the proper time of initiation, monitoring of the therapy, and its desirable effects on renal function with further restoration of diuretic agent responsiveness.

Key words: heart failure, renal replacement therapy, ultrafiltration, kidney injury, decongestion

The pathophysiology of congestion

Congestion is considered one of the most important pathophysiological mechanisms in heart failure (HF). Fluid overload is responsible for approx. 90% of the 1 million hospitalizations due to HF in the USA and Europe annually.[1] The initial accumulation of fluid is usually asymptomatic. However, increased intravascular volume, manifested by elevated central venous pressure, induces congestion and impedes flow in the renal veins, causing a net decrease in glomerular filtration. When acute heart disease leads to acute kidney injury (AKI), this condition is known as cardiorenal syndrome type 1 (acute CRS).[2] Congestion also causes the elevation of inflammatory markers, endothelial activation, as well as hepatic and intestinal disorders.[3,4] The adequate and complete management of congestion is vital for maintaining renal function, especially with regard to Na$^+$ excretion, and improves survival among patients with acute decompensated heart failure (ADHF),[5–7] regardless of transient increases in serum creatinine (sCr) levels. Another major concern associated with acute CRS is a decreased diuretic responsiveness due to the braking phenomenon. Moreover, hepatic dysfunction has been shown to predict worse outcomes in ADHF patients; thus, proper decongestion seems to be beneficial in this area as well.[8–10]

Differences between diuretics and ultrafiltration

The mode of action of diuretics and ultrafiltration (UF) differs significantly (Table 1). The biochemical composition of the urine produced by diuretic agents and the fluid produced by the UF procedure is one of the main distinctions between these treatments. Loop diuretics act in the ascending loop of Henle by antagonizing the Na/K/2Cl cotransporter; therefore, the activity of these agents is inherently linked with natriuresis.[11] By blocking sodium transport, diuretics create an osmotic gradient crucial for water reabsorption. The prolonged use of diuretics can lead to an impairment of natriuresis and the production of hypoosmotic urine. With reduced elimination of natrium, a reduction in intravascular water volume impairs fluid displacement from the interstitium. Proper natriuresis has been shown to be an essential factor for decongestion. Low sodium concentration in the urine or lack of a response to loop diuretics have been associated with a restricted diuretic response, increases in tubular injury markers, and a higher risk of all-cause mortality at one-year follow-up.[12,13] Moreover, diuretics are suspected to activate the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system, which can eventually result in a resistance to diuretics.[14] The precise management of fluid overload and forecasting fluid transfers for diuretic therapy still remains unclear.[15]

Conversely, UF seems to overcome the aforementioned pathophysiological issues seen with the use of diuretics. Ultrafiltration produced in an extracorporeal circuit is isosmotic with plasma, which results in higher natrium output, a reduction of central venous pressure and an increase in the renal pressure gradient.[16] The transition of fluid from the extravascular space reduces the symptoms of dyspnea and orthopnea, and improves lung mechanics and radiological signs of pulmonary edema.[17] Furthermore, the improvement in respiratory parameters with UF can last up to 6 months after treatment.[18] A reduction in pulmonary artery wedge pressure, as well as increase in cardiac output, diuresis and natriuresis without impacts on heart rate, systolic blood pressure (SBP), and electrolyte balance have been observed.[19] The UF conducted with proper filtration rates also diminishes neurohormonal and RAAS activation, and can cause abnormalities in this area only in the case of excessive fluid elimination. Moreover, the amount of cleared fluid and electrolyte parameters can be thoroughly controlled. Some of the disadvantages of UF are related to the extracorporeal circuit (Fig. 1), which requires anticoagulation, increases the possibility of bleeding, sometimes requires central venous access, and

Table 1. Comparison of loop diuretics and ultrafiltration

| Parameter	Diuretics	Ultrafiltration
Plasma norepinephrine level	increased	decreased
Cardiac output	variable	increased or unchanged
Mean arterial blood pressure	decreased	no change
Systolic blood pressure	not changed/decreased	not changed/decreased
Osmotic concentration of urine	hypoosmotic urine output	isoosmotic fluid removal
Predictability of fluid removal	unpredictable	accurate amount of fluid removal
Diuretic resistance	risk of development of diuretic resistance	reversing diuretic resistance
Risk of hypokalemia and hypomagnesemia	possible	not possible
Access	peripheral venous	peripheral or central venous
Anticoagulation	not necessary	necessary
Extracorporeal circuit	no	yes
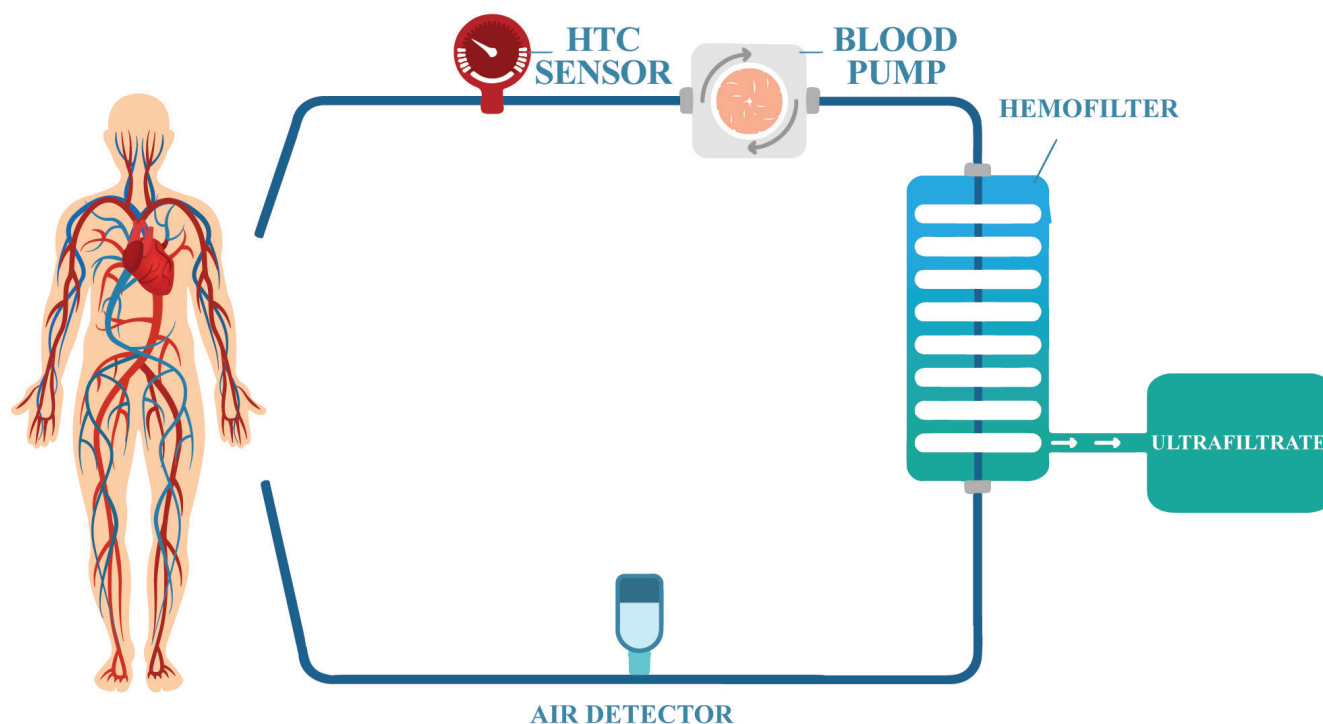
Fig. 1. Sample scheme of ultrafiltration circuit. Circuits can require single or double lumen cannulas inserted in peripheral venous access. Necessary pressure is created by the system of pumps. Ultrafiltrate is produced in hemofilter mostly due to convection process. Mass or volume of removed fluid is monitored. Circuit can be equipped with number of sensors such as hematocrit (HCT) or air detector. In modern machines, blood is usually withdrawn and returned to the same vessel

is associated with a higher incidence of catheter-related complications.[20] It is worth noting that there are also different modalities of renal replacement therapy (RRT), such as peritoneal UF, that can produce encouraging results and are cost-effective.[21] Regrettably, a detailed discussion of these methods is beyond the scope of this article.

Objectives

The increasing availability of UF devices prompted us to carry out a concise literature review of this treatment. Here, we review the published studies on UF and provide brief comments on their conclusions and shortcomings. We hope that this paper can help clinical physicians to reach an up-to-date perspective on the UF procedure, especially with regard to practical issues such as patient selection, choosing the most beneficial protocol, the proper time of initiation, and its desirable effects on renal function.

Clinical trials comparing UF and diuretic treatment

Appropriate decongestion remains essential for ADHF therapy. One of the most dangerous issues associated with the process of fluid removal is volume depletion, and a number of potential methods for monitoring this procedure have arisen. The safety and efficacy of one of them

– the Reprieve System – has been confirmed in TARGET-1 and TARGET-2 studies.[22]

As the theoretical beneficial effects of UF became noticed, this treatment was considered as an alternative to traditional therapy. Since the early 2000s, a number of clinical trials have been conducted to examine the safety and efficacy of UF in the treatment of ADHF (Table 2).

In the first randomized controlled trial (RAPID-HF), patients with chronic heart failure (CHF) were randomized into UF (n = 20) and standard care (SC; n = 20) groups. Weight loss after 24 h was the primary endpoint. The UF patients received a single eight-hour treatment at a rate chosen by the physician (up to 500 mL/h). Diuretics were held during UF, unless the physician decided to implement them. The volume removed at the time of the primary endpoint was larger in the UF group (4650 mL compared to 2838 mL, p = 0.001), and weight loss was also increased, but not significantly, in this group. The symptoms of dyspnea and CHF also improved more in the UF group. No significant differences in heart rate, blood pressure or electrolytes were observed between groups, and no serious complications, including acute kidney failure, occurred.[23]

Another single center, single-arm study (EUPHORIA) investigated 20 ADHF patients with sCr ≥ 1.5 mg/dL or diuretic resistance (≥80 mg furosemide) and fluid overload. Patients received UF at a fixed rate of 500 mL/h or, if SBP dropped to ≤80 mm Hg, the UF rate was reduced to 200 mL/h. The procedure was conducted until ADHF

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Table 2. Trials evaluating ultrafiltration for the treatment of acute decompensated heart failure (ADHF)

Study	RAPID-HF	EUPHORIA	UNLOAD	ULTRADISCO	CARRESS-HF	CUORE	AVOID-HF	Hanna et al.	Hu et al.
Year	2005	2005	2007	2011	2012	2014	2015	2012	2020
Rationale/ endpoint	safety and efficacy of UF	hospitalization time and WRF in UF	weight loss at 48 h	hemodynamic parameters during UF and SC	UF among ADHF with WRF	rehospitalization rate for HF at 1 year	time to first HF event in UF and SC group	time to PCWP maintain ≤18 mm Hg for a minimum of 4 h	efficacy and safety of UF and SC
Inclusion criteria	HF, congestion, no EF cutoff	ADHF, renal insufficiency or diuretic resistance, congestion, no EF cutoff	ADHF, congestion, no EF cutoff	ADHF, congestion, no EF cutoff	ADHF, WRF, congestion, no EF cutoff	NYHA III/IV, estimated fluid overload ≥4 kg in 2 months, EF ≤ 40%	ADHF, congestion, no EF cutoff	NYHA III/IV, EF < 40%, PCWP ≥20 mm Hg	ADHF, congestion, no EF cutoff
Valvular heart disease	severe stenosis excluded	no information	no information	severe stenotic excluded	severe stenosis excluded	no information	severe stenosis excluded	severe aortic stenosis/regurgitation, severe mitral stenosis excluded	severe mitral or aortic stenosis, tricuspid disease excluded
Follow-up	90 days	90 days	90 days	36 h	60 days	1 year	90 days	90 days	90 days
Patients	40	20	200	30	188	56	224	36	100
UF parameters	single 8 h procedure, rate determined by physician	rate determined by protocol, duration determined by physician	duration and rate of UF determined by physician	rate determined by protocol, duration determined by physician	fixed UF rate – 200 mL/h, duration determined by physician	duration and rate of UF determined by physician	protocol-based UF rate and duration	UF rate of 400 mL/h for 6 h, then 200 mL/h	rate and duration determined by physician
Diuretics during UF	no	no	no	no	no	yes	no	no	no
Results	fluid loss greater in UF group	reduction of length of stay and readmissions, positive effect for 3 months in UF	greater weight loss and reduced amount of rehospitalizations in UF	greater improvement in hemodynamic parameters, NT-proBNP, aldosterone in UF	higher increase in creatinine level, with no advantage in weight loss in UF	longer stabilization and smaller number of rehospitalizations in UF	trend toward longer time to first HF event in UF	UF is a safe method, can remove fluid faster than diuretics and can lead to shorter hospitalization	better volume control and higher urine output increase in UF

UF – ultrafiltration; WRF – worsening renal function; SC – standard care; NT-proBNP – N-terminal brain natriuretic peptide; PCWP – pulmonary capillary wedge pressure; EF – ejection fraction.

symptoms were resolved. Weight decreased significantly and remained lower until the end of the follow-up period (90 days). An improvement in global clinical status and brain natriuretic peptide (BNP) parameters were also noticed. The EUPHORIA patients' hospitalization time was about 4.3 days shorter than those in the ADHERE registry.[24] The study also showed that aggressive fluid removal (8500 mL using UF) did not provoke worsening renal function (WRF), electrolyte abnormalities or hypotension.[25] An interesting aspect of the EUPHORIA study is that in the 3 months preceding UF, 9 patients required hospitalization, and after the procedure, only 1 needed hospitalization in the same period following UF. These results are consistent with previous studies.[26] The aforementioned improvement can be explained by a reversal of "braking phenomenon" caused by a "diuretic holiday".

An additional multi-center randomized controlled trial that was supposed to confirm the efficacy of UF in ADHF treatment was the UNLOAD study. Two hundred patients hospitalized due to ADHF and presenting with symptoms of hypervolemia were enrolled. Diuretic agents were prohibited during first 48 h after enrollment in the UF arm. The filtration rate and length of the procedure were adjusted by the physician up to 500 mL/h. Patients in the SC arm were treated with loop diuretics, according to the protocol, and the dose had to have been at least doubled in comparison to the pre-hospitalization dose. The primary endpoints were weight loss and dyspnea assessment at 48 h after randomization. At the time of the endpoint, patients enrolled in the UF group achieved greater weight and net fluid loss. Dyspnea scores were comparable across groups. The results of UNLOAD confirmed

the results of EUPHORIA and showed that UF patients at the 90 day follow-up had fewer rehospitalizations due to HF, rehospitalizations, rehospitalization days, and unscheduled visits. No sCr changes at 90 days and a lower incidence of episodes of hypokalemia were also observed in the study group. The authors suggested that the lack of an association between net fluid loss and sCr levels can imply a loop diuretics contribution to renal dysfunction, which propels HF progression.[27]

One small, randomized study, ULTRADISCO, was performed by Giglioli et al.[28] Patients were assigned to UF and SC groups, and were monitored using PRAM[29] – a device that allows investigators to conduct noninvasive measurements of hemodynamic variables. The UF group received the procedure at a protocol-based rate, adjusted to SBP (SBP < 100 mm Hg meant an UF rate of 100 mL/h; 100 mm Hg < SBP < 110 mm Hg meant an UF rate of 200 mL/h; SBP > 110 mm Hg meant an UF rate of 300 mL/h). The duration of the procedure was left to the discretion of the physician. Patients treated with UF had a greater decrease in parameters such as N-terminal proBNP (NT-proBNP) and aldosterone. Arterial pressure parameters remained unchanged during the UF procedure and decreased significantly after diuretics infusion, suggesting a better hemodynamic stability with UF treatment. A number of cardiac parameters also showed greater improvement in the UF group (stroke volume index, cardiac index, cardiac power output, cardiac cycle efficiency, systemic vascular resistance).

The CARRESS-HF was the most concerning study published to date, and raised many doubts about the safety and efficacy of UF. One hundred and eighty-eight patients were enrolled in this study, equally distributed across the pharmacotherapy and UF arms. All of the participants were hospitalized because of HF, had worsened renal function (defined as increase of sCr ≥ 0.3 mg/dL within 12 weeks before or 10 days after admission) and signs of hypervolemia. Diuretics were not administered during the UF treatment. The UF rate was configured to 200 mL/h in every patient; however, it could be slowed or discontinued by the physician. No protocol for implementing changes in UF was provided. Patients assigned to the pharmacotherapy arm were administered diuretics in doses adjusted to achieve production of 3–5 L of urine daily. The SCr change and weight loss at 96 h after randomization were the primary endpoints. A greater increase in sCr levels was observed in the UF group, but there were only non-significant differences seen in weight loss. In addition, a higher percentage of UF patients had serious adverse effects.[20]

The results and methodology of the CARRESS-HF study raised major concerns. First, 39% of the UF group received diuretics instead of UF (9%), or received diuretics after the UF was stopped (30%). Clearly, these procedures can strongly impair the assessment of adverse effects in both groups. In addition, therapy in the diuretics group was titrated based on urine output, while the UF rate was mandated to be 200 mL/h for every patient in this group. Such a rigid approach to UF without recalibrating the circuit to the clinical situation remains controversial.[30] A recent per-protocol analysis of the CARRESS-HF trial has shed additional light on the shortcomings of this study.[31] This protocol analysis revealed that UF group patients, who actually received their randomized treatment, had a significantly higher net fluid loss and reduction of weight. The UF treatment was also associated with lower serum sodium levels. This analysis also confirmed a higher level of sCr in the UF group. However, recent studies have shown that a transient increase in sCr can be the result of better decongestion and a decrease in renal flow, and can even predict a better outcome.[32] Moreover, 90% of the UF group was not properly decongested at the assessment of the primary endpoint.[1] At 96 h after start of the therapy, only 32% of UF patients were still included in the study compared to 80% in the diuretic group, and reasons for the withdrawal of patients from the UF group were likely not clinically driven.[33] Another problem with the trial was the adjustment of UF rates, which was primarily set at 200 mL/h. The per-protocol analysis showed that these rates were actually much lower and, more importantly, the timing of the adjustments is a matter of concern. Common consensus, stemming from the Frank–Starling law, suggests using high UF rates at the beginning of the procedure in order to achieve the highest possible transfer from the interstitial space and then reducing the rate in the case of hypotonia or other complications. The opposite approach can lead to suboptimal decongestion and deteriorate prognosis, which is what was observed in the CARRESS-HF study, where, in contrast to the results of UNLOAD, the 60-day outcome did not differ in both arms.[1]

The results of the CARRESS-HF trial encouraged investigators to conduct another study where the UF rate would be adjustable. The CUORE trial was a small, single-center study where 56 patients were randomized into 2 arms – SC and UF. The participants were observed for 1 year and rehospitalization for CHF was the primary endpoint. The control group was treated with loop diuretics according to guideline recommendations, and the UF group received up to 2 sessions of UF, and up to a cumulative fluid removal >2 L. The physicians were encouraged not to exceed 75% of initial weight increase. An interesting observation in this study is that diuretic administration was maintained in both groups. The time and rate of UF was left to discretion of the treating physician. Peripheral and pulmonary edema, and the New York Heart Association Functional Classification (NYHA) stage improved similarly in both groups. Doses of furosemide, hospitalization time and absolute body weight reduction did not differ. At the six-month follow-up, average body weight, renal function and furosemide dose did not change compared to discharge in the UF group, while these variables worsened in the control group. The BNP levels were also reduced in the UF group, but remained unchanged in the control group. Four hospitalizations occurred in the UF group,

whereas 30 were observed in the control group.[34] The results of the CUORE trial are consistent with UNLOAD and indicate that that a prolonged protective effect of UF can last for up to 6 months. The authors of the CUORE study also suggested that decongestion is not the only key to outcome improvement. As the amount of the fluid removed was similar in both groups, the improvement may be attributable to the quality of the withdrawn fluid.

The promising results of the CUORE study prompted researchers to carry out larger, randomized control trials with adjustable diuretic and UF doses.[35] The AVOID-HF is the most recent randomized multi-center study. This study was designed to randomize 810 HF hospitalized patients and was prematurely finished with 224 patients.[36] One hundred and sixty-five patients were observed until the end of follow-up. The study included ADHF patients who presented with symptoms of fluid overload.[37] Patients were evaluated at 30, 60 and 90 days following discharge. Doses of loop diuretic in the pharmacological arm and UF rates in the UF arm were established on the basis of a protocol prepared by the investigators.[37] The supply of diuretics was stopped during UF. The time to a HF-related event, defined as HF rehospitalization, unscheduled visits, or emergency treatment with intravenous loop diuretics or UF, was the primary endpoint. Due to the relatively short length of the study, significant differences in the survival curves were not observed. At 90 days post-treatment, 25% of the UF group and 35% of the pharmacotherapy group experienced a HF event. However, the suggested 37% risk reduction in HF events in the UF group did not reach statistical significance. The UF group also exhibited a greater net fluid loss. Weight loss at 72 h, total weight loss during hospitalization, time to freedom of congestion, and the percentage of patients free from congestion at discharge did not reach statistical significance, albeit greater improvement was noticed in the UF group. Within 30 days after discharge, patients in the UF group had, per day at risk, fewer rehospitalizations for HF, fewer HF rehospitalization days, lower rehospitalization rates due to a cardiovascular (CV) incident, fewer rehospitalization days due to a CV incident, and fewer rehospitalizations due to a CV incident. The findings of the AVOID-HD trial are consistent with the UNLOAD results and confirm that early UF, implemented before WRF, has a beneficial, prolonged effect on decongestion.[36]

There were also several smaller and less known studies conducted. The first of them, conducted by Hanna et al.,[19] included 36 patients. The primary endpoint for this study was a decrease in pulmonary artery wedge pressure less than 18 mm Hg for 4 consecutive hours. The results confirmed the findings from larger studies. The UF group tended to reach the primary endpoint faster than the pharmacotherapy group, achieved a greater weight reduction and a higher total volume was removed, and their hospitalization was shorter. Kidney function, biomarkers and adverse events did not differ.

Another study, conducted by Hu et al.,[38] enrolled 100 patients with ADHF. Patients were randomized into 2 groups: early UF (n = 40) or torsemide plus tolvaptan (n = 60). The UF rate and duration of the procedure was managed by the physician. The initial UF rate was set to 200–300 mL/h and then reduced. On the 4th day after initiation of the treatment, UF was terminated and UF patients received torsemide with tolvaptan at the same mean dose that was administered to the pharmacotherapy group. At day 3, UF patients exhibited greater weight loss and a urine increase. After 8 days, patients who received UF presented with increased weight loss and urine output, and decreased BNP levels, NYHA scores, jugular venous pulse scores, and inferior vena cava diameters. No differences in re-admissions and mortality at 1 and 3 months follow-up were observed; however, the three-month readmission rate was lower in the UF group, which may have reached statistical significance in a larger study.

Two meta-analyses were also conducted to evaluate the value of UF therapy among acute HF patients. The first included 7 articles and 771 patients,[39] and showed that UF leads to greater weight loss, fluid removal and better HF rehospitalization rates, with comparable effects on renal function. The UF, however, did not have impact on mortality. A more recent meta-analysis, carried out in 2020, included 8 trials and 801 participants. The results showed greater fluid removal and weight loss, and lower incidence of worsening HF and rehospitalizations for HF, without effects on renal function and all-cause mortality.[40] Regrettably, neither of these studies evaluated the incidence of adverse effects, such as catheter related infections, filter clotting, etc.

Proper time of initiation and selection of patients

Precisely distinguishing patients who will benefit from UF remains a challenge. The high cost and potential adverse effects restrict the use of UF as a global method for fluid management in HF patients. The current American and European cardiology guidelines do not provide clear information regarding who should undergo this procedure, suggesting that it should be restricted to patients with resistance to diuretics therapy.[41,42] The American guidelines do indicate that UF may be considered to alleviate symptoms in patients with fluid overload (level of evidence B), while the European guidelines focus more on the aspect of renal failure and propose that UF should be considered in patients with congestion and AKI (level of evidence C). The aforementioned guidelines also suggest the following criteria to help qualify patients for UF: hyperkaliemia >6.5 mmol/L, pH < 7.2, serum urea level >25 mmol/L, and sCr > 3.4 mg/dL.

The lack of a clear definition for diuretic resistance creates additional issues. Ter Maaten et al.[14] have proposed

a three-part definition for diuretic resistance which includes persistent congestion despite administration of >80 mg of furosemide per day, amount of excreted sodium below 0.2% of filtered load, and failure to excrete at least 90 mmol of sodium within 72 h of 160 mg furosemide given twice daily. Notwithstanding this definition, persistent congestion with diuretic resistance implies a severe outcome and UF can serve as a rescue therapy.

Another issue is the time of the implementation of RRT in the context of renal function. The ELAIN trial compared early and delayed initiation of RRT in patients with stage 2 AKI. Patients were randomized to receive an immediate initiation of RRT (hemodiafiltration) or to wait until absolute indications occurred, or AKI progressed to stage 3. Patients in the early group had decreased all-cause mortality at 90 days compared to the delayed group (39.3% compared to 54.7%, p = 0.03).[43] However, the findings of this study have to be treated with caution because of the different RRT modality and the distinct population of patients. Nonetheless, the results suggest that RRT should be implemented sooner than later in in diuretic-resistant renal worsening patients. Moreover, these studies did not include sufficient data about the use of UF in patients with different types of HF or valvular heart disease.

Choosing the most effective protocol

Selection of the most effective UF protocol and deciding its duration raises many doubts among clinicians. The cardiological, nephrological and intensive care medicine guidelines of European and American scientific associations do not propose a consistent protocol for UF, especially for patients with ADHF. The unique standards that have been recommended by Kidney Disease: Improving Global Outcome and European Society of Intensive Care Medicine, are tailored for patients with AKI and suggest using an effluent volume of 20–25 mL/h/kg for post-dilution CRRT[44] and a 20 mL/kg/h clearance rate for small solutes.[45] Additional information about the recommendations proposed by these guidelines is shown in Table 3. Due to the different clinical constellations of ADHF patients in comparison to AKI group, these instructions need to be treated with caution.

Studies have clearly shown that UF parameters have to be tailored precisely for every patient. The CARRESS-HF trial, where same rate was used for all patients, manifested no difference in the weight loss and rehospitalizations, with a higher increase in sCr in the UF patients group. Conversely, the UNLOAD, ULTRADISCO, CUORE, and AVOID-HF studies, where parameters were adjusted by the physician or were protocol-based, showed that UF patients had fewer rehospitalizations or that their hemodynamic parameters were improved in comparison to SC group, with no difference in sCr. Interestingly, the mean UF rates used in the UNLOAD, CUORE and AVOID-HF trials were higher than in the CARRESS-HF study, suggesting that the outcome for sCr in these studies should be worse. This can be explained by the adjustment of the protocol; not tailoring procedure parameters can create a situation where some groups of patients are excessively dehydrated, leading to hypovolemia, and others remain congested due to lower than needed fluid removal.[33] Furthermore, protocol analysis of the CARRESS-HF study[31] showed the that the mean UF rates provided in the study were 83 mL/h, 140 mL/h, 107 mL/h, and 70 mL/h for every sequencing 24 h period, respectively. The UF rates should be maximized at the beginning of the procedure and then maintained or reduced. This conclusion stems from 2 rationales. The first derives directly from the Frank–Starling law. The process of refilling intravascular space from

Table 3. Guidelines-based recommendations from European, American, Canadian, and Japanese scientific associations on the fields of cardiology, nephrology and intensive care

Association	Information about UF in ADHF	Level of evidence
European Society of Cardiology	May be considered in refractory congestion/Should be considered in refractory volume overload and AKI	IIbB/IIaC
American College of Cardiology Foundation/American Heart Association	May be considered for fluid overload to alleviate symptoms/May be considered for refractory congestion	B/C
Canadian Cardiovascular Society	Not recommended for the routine use in intractable congestion	Weak recommendation, low-quality evidence
Japanese Circulation Society	Patients with renal dysfunction and refractory congestion should receive CRRT, all modalities have equal evidence level	IIbB/IIaC
European Renal Association – European Dialysis and Transplant Association; Kidney Disease Improving Global Outcome; Canadian Society of Nephrology; Japanese Society of Nephrology; European Society of Intensive Care Medicine; Society of Critical Care Medicine; Canadian Critical Care Society; The Japanese Society of Intensive Care Medicine	No guidelines for ADHF patients	–

UF – ultrafiltration; ADHF – acute decompensated heart failure; AKI – acute kidney injury; CRRT – continuous renal replacement therapy.

the interstitium decreases with the amount of removed fluid. Hence, the UF rate should be maintained or reduced during the procedure in order to allow the plasma refilling rate to keep up with the fluid removal rate. Proceeding in such a fashion preserves volume depletion and hypotension, and leads to better decongestion, which should be primary target of the treatment as the incomplete decongestion is associated with worse outcomes.[32,46,47] Indeed, in the CARRESS-HF study, 90% of the patients were not properly decongested. In other studies, where dehydration was increased, improvement of the outcome, in the context of rehospitalizations, has been observed.[27,34,36] Secondly, such low rates of UF can cause a higher incidence of filter clotting,[48] and the percentage (36% of patients) of filter clotting in the CARRESS-HF study was unprecedented in comparison to other studies.

At the time of the writing of this article, 1 randomized controlled trial had used loop diuretics during UF. The CUORE trial investigated UF patients with no diuretic gap, in a one-year follow-up, and reported a reduction in HF rehospitalizations and a non-significant trend towards lower mortality in comparison to the SC group. A diuretic holiday is suspected to reverse the breaking phenomenon and to reduce diuretic-induced neurohormonal activity, thus making such an approach controversial.[26] Nevertheless, the process of the braking phenomenon is not fully understood. It is probable that some of its components, such as the proliferation of distal convoluted tubule, which is documented in rats,[49] can be irreversible or irreversible by the short period of time of the diuretic holidays. Future studies, like three-arm randomized control trials with SC, UF only and UF with diuretics, may be worth considering. Presuming that a diuretic holiday is beneficial for ADHF patients, the idea of implementing regular, preventive UF for patients with congestive HF should be investigated, especially given the potential reduction of hospitalizations shown in previous studies and the high cost of in-patient care.[1]

Targets for decongestion

A number of different methods to evaluate the proper level of decongestion have been proposed. The most basic is the assessment of dry weight with an attempt to reach it exactly or a pre-specified percentage of it. This approach was used in the CUORE trial.[34] Increased central venous pressure, which was identified as threat for renal function, and is a neurohormonal, inflammatory and endothelial cell activator,[3] can also constitute a target for a treatment. For obvious reasons, the invasive measurement of central venous pressure cannot be applied for every UF patient. However, it can be approximated using ultrasonography by measuring the collapsibility index of inferior vena cava.[50] It must be noted, however, that the reliability of this measurement can be limited by respiratory mechanics,

ventilation with positive pressure, elevated pulmonary artery pressure, valvular disease, and the skill of the physician performing the examination. The safety and efficacy of evaluating pulmonary artery pressure by the implantable wireless device CARDIOMEMS has been confirmed in a CHAMPION trial,[51] and has been shown to reduce HF hospitalizations.

Monitoring therapy and preventing volume depletion

Online monitoring of hematocrit is the obvious method for preventing volume depletion during UF. This technique has been successfully used in the CUORE trial.[34] Limits that would automatically stop the UF procedure due to an excessive hematocrit increase can also be programmed. While hematocrit assessment can help estimate volume loss, many factors including position change or bleeding can interfere with measurement of this parameter. Attempts to use whole body bioimpedance to assess tissue hydration have also been successful,[52] but this technique is not yet popular in clinical practice. A recent study has shown that the μCor system, which was tested on patients undergoing dialysis, part of whom suffered from HF, can assess thoracic fluid using radiofrequency.[53] Regrettably, none of the aforementioned methods are completely satisfactory.

Concerns about renal function during UF

The CARRESS-HF study reported a higher increase in sCr in the UF group compared to the diuretic group. Moreover, 16% of UF termination cases in this trial were caused by an increase in sCr. This finding seems to suggest that UF is associated with worsening renal function. However, there are many studies concluding that this approach can be justifiable in 2 dimensions. First, an increase in sCr in patients being decongested can be caused by number of different factors, and the increase should be judged in conjunction with the particular clinical constellation. The associations between increased sCr and renal tubular damage are also questionable. The ROSE-AHF trial examined the correlations between sCr and markers of tubular damage such as neutrophil gelatinase associated lipocalin (NGAL), N-acetyl-β-D-glucosaminidase (NAG) and kidney injury molecule-1 (KIM-1), and reported only low correlations.[47] Another study suggests that the evaluation of renal function through the prism of creatinine levels in decongested patients with ADHF can be misleading. Instead, this study proposed assessing spot urinary sodium levels, as decreases during the therapy were predictive of worse outcomes.[12] Furthermore, in the DOSE trial, an increase in sCr was found to be a predictor of better

outcomes in HF patients during decongestion.[32] A possible explanation for this finding is that the increase of sCr is due to better decongestion. The ROSE-HF also showed that that an increase in NGAL, NAG and KIM-1 was associated with improved survival. This finding suggests that some degree of tubular injury is acceptable in an endeavor to reach maximal decongestion. On the other hand, there are papers that suggest that a NGAL increase is not associated with volume depletion, so it could be more precise parameter than creatinine to evaluate kidney function during UF.[54] The essential thing about considering UF in ADHF in the context of renal function is to use a clinical-based approach. There is a major shortfall in evidence to prove beyond any reasonable doubt that transient WRF during the UF treatment is sufficient to abandon the therapy. Hence, the decision continue or discontinue therapy should be made individually in every case.

Conclusions

Ultrafiltration is a safe and effective method for decongestion in patients with ADHF. The effectiveness of this therapy for removing fluid, reducing HF events and decreasing the number of subsequent hospitalizations has been demonstrated in a number of clinical trials. The role of diuretic treatment as a standard therapy is unquestioned. However, UF can also serve as an alternative method for diuretic-resistant patients, without greater concern for a worsening of renal function.

Ultrafiltration obviously still needs to be carefully examined. An issue that is essential for future successful treatment with this method is the creation of precise algorithms for qualification and the selection of patients who will benefit from this procedure. Another issue that needs to be addressed is the timing of the implementation of UF in the context of renal function. Assessment of glomerular and tubular injury, and the use of specific biomarkers during UF, should also be further evaluated. There are also concerns regarding the best UF protocol to use for fluid overload patients and the role of diuretic use during the procedure needs more study. Ultrafiltration has multiple theoretical benefits such as not contributing to electrolyte abnormalities, diminishing neurohormonal and RAAS activation, and possibly reversing the "braking phenomenon". The results of numerous trials show its safety and efficacy in fluid removal, and suggest a potential beneficial clinical effect in reducing the number of HF rehospitalizations. This trend requires further carefully designed trials to be confirmed. The prospects of implementing regular, preventive UF for HF congestive patients are distant, but worth imagining. The effects of this treatment on cardiovascular and all-cause mortality also have to be investigated in larger studies. In addition, the incidence, severity and management of adverse effects, such as thrombotic events, bleeding and filter clotting, require more precise investigation.

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