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MINIREVIEWS

Extracorporeal veno-venous ultrafiltration in congestive heart failure: What's the state of the art? A mini-review

Andrea Urbani, Filippo Pensotti, Andrea Provera, Andrea Galassi, Marco Guazzi, Diego Castini

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Abstract

Hospitalizations for heart failure exceed 1 million per year in both the United States and Europe and more than 90% are due to symptoms and signs of fluid overload. Rates of rehospitalizations or emergency department visit at 60 days are remarkable regardless of whether loop diuretics were administered at low *vs* high doses or by bolus injection *vs* continuous infusion. Ultrafiltration (UF) has been considered a promising alternative to stepped diuretic therapy and it consists in the mechanical, adjustable removal of iso-tonic plasma water across a semipermeable membrane with the application of hydrostatic pressure gradient generated by a pump. Fluid removal with ultrafiltration presents several advantages such as elimination of higher amount of sodium with less neurohormonal activation. However, the conflicting results from UF studies highlight that patient selection and fluid removal targets are not completely understood. The best way to assess fluid status and therefore establish the fluid removal target is also still a matter of debate. Herein, we provide an up-to-date systematic review about the role of ultrafiltration among patients with fluid overload and its gaps in daily practice.

Key Words: Fluid overload; Ultrafiltration; Diuretics; Heart failure

Core Tip: This mini review aimed to evaluate the role of ultrafiltration in congestive heart failure and to compare this approach to standard therapy essentially based on diuretics. Evidences are still controversial and matter of debate, however it is clear that the use of ultrafiltration has beneficial effects on outcomes such as rehospitalization for heart failure and symptoms attenuation. This review of the literature also highlighted the pivotal role of a non-invasive multiparametric assessment of fluid overload to guide physicians through tailoring patient's decongestion.

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INTRODUCTION

Hospitalizations for heart failure (HF) exceed 1 million per year in both the United States and Europe and more than 90% are due to symptoms and signs of fluid overload. In addition, up to 1 in 4 patients (24%) is readmitted within 30 d and 50% of patients are readmitted within 6 mo[1,2]. Recurrent fluid overload in HF has uniformly been associated with worse outcomes independently of age and renal function[3]. Data from the Diuretic Optimization Strategies Evaluation trial show that 42% of patients with acutely decompensated HF reached the composite end point of death, rehospitalizations or emergency department visit at 60 d regardless of whether loop diuretics were administered at low *vs* high doses or by bolus injection *vs* continuous infusion[4]. Therefore, the need for adjunctive treatment strategies to standard stepped diuretic therapy in patients presenting with fluid overload in the context of decompensated HF is critical. One promising therapy is extracorporeal veno-venous ultrafiltration (UF). Ultrafiltration consists in the mechanical, adjustable removal of iso-tonic plasma water across a semipermeable membrane with the application of hydrostatic pressure gradient generated by a pump [5].

The fluid removed from the intravascular compartment is constantly replaced by fluid from the third space configurating the so called "intra-vascular refill" phenomenon, thus allowing gradual and controlled fluid overload resolution[6]. Despite fluid removal with UF presents several advantages such as elimination of higher amount of sodium with less neurohormonal activation, results from clinical studies regarding efficacy and safety have been variable.

Herein, we provide an up-to-date systematic review about the role of UF among patients with fluid overload and its gaps in daily practice.

PATHOPHYSIOLOGY AND CONSEQUENCES OF FLUID OVERLOAD

The initial trigger of fluid overload is a reduced cardiac output that results from failing myocardium. This process causes an arterial hypovolemia which triggers a cascade of events designed to increase intra-arterial blood volume. The main mechanism involved is a neurohumoral activation of the renin-angiotensin-aldosterone (RAAS) axis that increases renal and sodium avidity, thereby resulting in an increase of effective blood volume. In a setting of HF, proximal sodium and water retention are so elevated that distal nephron chronically undergoes low sodium delivery, maintaining persistent RAAS activation[7]. Also, increased sympathetic tone leads to splanchnic arterial and venous constriction resulting in blood redistribution from the splanchnic capacitance vasculature to the circulatory volume. This expands the effective circulating volume by redistribution in a setting where volume expansion is already ongoing[8]. At the beginning, these changes occur as compensatory mechanisms to maintain effective circulating blood volume, over time they become harmful with the development of pathological inappropriate blood volume and interstitial fluid expansion contributing to fluid overload and organ congestion. An excessive effective circulating blood volume leads to hemodynamic congestion with increased central filling pressures[9]. Deranged hemodynamics and neurohormonal activation leading to excessive tubular reabsorption produce long-standing venous congestion. Elevation of central venous pressure is rapidly transmitted to the renal veins, causing increased interstitial and tubular hydrostatic pressure that decrease net glomerular filtration[10]. Hence, in this context, venous congestion of the kidneys rather than arterial underfilling is associated with decreased renal blood flow and an increase in creatinine[6,11]. Moreover, congestion within peripheral vascular tissues can produce endothelial activation followed by up-regulation of inflammatory cytokines, which promotes additional fluid retention[12,13]. Therefore, reducing congestion should be the foremost goal in patients with HF and fluid congestion[6].

DETECTING FLUID OVERLOAD IN HF

Historically, the gold standard to evaluate fluid overload has been pulmonary artery catheterization (PAC) that allows a direct measurement of right atrial pressure and pulmonary capillary wedge pressure (PCWP)[14]. For several years it has been widely used but then, Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness trial showed that the use of PAC to guide diuretic therapy in comparison with serial clinical assessment did not improve mortality[15]. Currently, due to its invasive nature and the lack of evidence, the use of Swan Ganz catheterization is restricted to a selected group of critically ill patients in tertiary hospitals with high level of user competence.

For what concern the non-invasive assessments of congestion, a multiparametric point of care ultrasound (POCUS) can play a key role. In the Figure 1, we make a comprehensive list of all the most used POCUS parameters.

Lung ultrasound (LUS) can be used to assess interstitial oedema and pleural effusion in patients with known or suspected HF and detects the so-called B-lines that originates from the extravascular fluid[16,17]. B-lines are hyperechoic artefacts which appear as vertical lines originating from the pleural surface [18]. More than three B-lines in more than two intercostal spaces bilaterally are considered diagnostic of interstitial and alveolar oedema in acute HF[8,19]. In comparison to chest X-ray, lung ultrasound is more accurate for the diagnosis of interstitial oedema and HF, although B-lines can occur in other condition such as interstitial lung disease and non-cardiogenic pulmonary oedema[16,20,21]. Echocardiography can, also, be used to non-invasively and quickly estimate right and left-sided filling pressure. An appraisal of the right atrial pressure can be performed by evaluating the collapsibility and width of the inferior vena cava (IVC)[22]. Any variation in right atrial pressure is transferred backward, and modifies IVC size, in fact a significant increase in right atrial pressure, as seen in HF, would eventually result in IVC distention. Pulsed doppler and tissue Doppler are useful tools in estimating left-sided filling pressure. The E/e' ratio > 14 has high specificity for increased filling pressures, especially if E-wave deceleration time is short and A-wave velocities are low[23,24]. Furthermore, congestion and high central venous pressure lead to increased renal interstitial pressures that affects primarily renal venous flow which can be evaluated with Doppler ultrasound. Specifically, the presence of an intermittent renal venous flow rather than continuous as in healthy subjects has been strongly related with an increased central venous pressure measured invasively and has been associated with a worse prognosis in both acutely decompensated HF and among stable patients with chronic HF[25,26]. Despite diagnosis of congestion is currently made with the combination of signs and symptoms, a suggestive X-ray and the measurement of elevated natriuretic peptides (NPs), these additional non-invasive POCUS-guided approach can increase the accuracy of the diagnosis and, more importantly, can be helpful in tailoring patient's decongestion during the hospitalization (Table 1).

USE OF DIURETICS IN ACUTE HF AND DIURETIC RESISTANCE

Diuretic agents, especially loop diuretics, have been for decades the backbone of the therapy for fluid overload[30,31]. Guidelines recommend the use of intravenous loop diuretic rather than oral as first line therapy and an early as possible administration because of its association with reduced in-hospital mortality[32]. The initial diuretic regimen depends on whether the patient is diuretic naïve or not. In fact, diuretic naïve patients should receive an initial dose of at least 20-40 mg of intravenous furosemide, whereas patients already on an ambulatory diuretic regimen should receive 1-2 times the 24-h home dose intravenously. A spot urine sodium content of > 50-70 mEq/L and an hourly urine output of > 100-150 mL during the first 6 h usually identifies patients with an initial acceptable diuretic response[33,34]. If these targets are not reached, a prompt doubling of loop diuretic dose is usually required and should be repeated until maximal dose of loop diuretics is administered; as maximal dose of loop diuretic is given, an addition of another diuretic agent should be considered as increasing the loop diuretic dose does not improve natriuresis any further. Despite diuretics are highly effective in the early stages of acute HF, in a significant subset of patients loop diuretics become increasingly ineffective with disease progression due to the onset of diuretic resistance[35]. A recent definition of diuretic resistance has been proposed which implies a failure to increase fluid and sodium (Na+) output sufficiently to relieve volume overload, edema, or congestion, despite escalating doses of a loop diuretic to a ceiling level (80 mg of furosemide once or twice daily or greater in those with reduced glomerular filtration rate or HF)[36]. Diuretic resistance is the result of several factors such as impaired absorption, decreased renal blood flow, hypoalbuminemia and proteinuria, all leading to a reduced levels of active diuretics in the tubular lumen[35,37]. Unfortunately, clinical signs and symptoms are often unreliable to detect diuretic resistance. A poor diuretic response predicts mortality rate after discharge, subsequent rehospitalization, or renal complications from congestive HF[36]. Therefore, finding more effective treatments for fluid removal is an unmet need.

Table 1 Differences between ultrafiltration and diuretics

Loop diuretics	Isolated ultrafiltration
Hypotonic urine	Isotonic plasma water
Direct neurohormonal activation	No direct neurohormonal activation
Unpredictable elimination of sodium and water	Precise control of rate and amount of fluid removal
Diuretic resistance	Restoration of diuretic responsiveness
Hypokalemia and hypomagnesemia	No effect on plasma concentration of potassium and magnesium
No need for anticoagulation	Need for anticoagulation
No extracorporeal circuit	Need for extracorporeal circuit

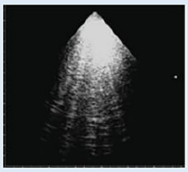
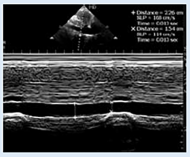
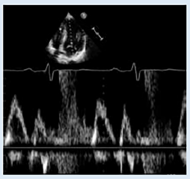
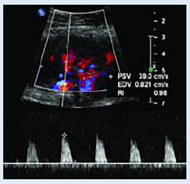
Parameters assessed by POCUS indicative of fluid overload	Echographic windows and transducer positions	Pathological reference values	Clinical and prognostic significance	Ref.
B-Lines 	8 chest zones measured with phased-array or curvilinear transducer placed in the intercostal spaces	A cut off-value of ≥ 3 B-lines in at least two intercostal spaces per hemithorax	Indicates interstitial oedema and identifies acute HF in patients with dyspnea with high sensitivity (94%-97%) and specificity (96%-97%)	[27]
IVC size 	Subcostal view with curvilinear or phased-array transducer at 1.0 to 2.0 cm from the junction with the right atrium	An IVC smaller than 21 mm that collapses more than 50% is considered normal	It might detect increasing intravascular volume even prior to any change in symptoms or body weight	[28]
Doppler left sided filling pressure (E/e' ratio) 	Apical 4-chamber view with Doppler imaging and tissue doppler	E/e' ratio > 14	It indicates rising filling pressure especially if E deceleration time is short and A-wave velocities are low	[23]
Doppler Intermittent renal venous flow 	Left lateral decubitus position using a convex or sector transducer aligned with the lowest intercostal space offering a longitudinal view of the right kidney	When central venous pressure increases, renal venous flow becomes firstly pulsatile and then biphasic	It is an earlier marker of development of congestion and suggests a poor prognosis	[29]

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Figure 1 Direct and indirect non-invasive estimation of fluid overload with point of care ultrasound. IVC: Inferior vena cava; POCUS: Point-of-care ultrasound; HF: Heart failure.

HOW DOES VENO-VENOUS UF WORK?

As briefly described in the introduction, the mechanism of action of UF is based on the use of a transmembrane pressure gradient generated by a pump, which through a semi-permeable membrane causes the removal of plasma water from whole blood. The net effect at the end of the process is the achievement of an isotonic concentration between the ultrafiltrate and the plasma water removed from the circulation[10].

UF requires a venous access to fulfill the filtration process through the hemofilter and the subsequent reintroduction of the ultrafiltered plasma into the systemic circulation[38].

Optimal anticoagulant therapy by continuous infusion of heparin is also required to preserve the function of the filter during the whole process.

The Figure 2 schematically shows the UF process; the blood, after being extracted from the patient by venous access, is transferred to the extracorporeal circuit of the UF and then reintroduced into the bloodstream.

Newer devices allow, *via* a double-lumen venous catheter placed in the jugular or basilic vein, a blood draw with minimal recirculation.

There are various methods by which the UF process can be achieved: isolated UF, hemofiltration and UF in combination with dialysis.

Isolated UF is only a method of fluid control, whereas all the others can simultaneously achieve a certain degree of blood purification with different mechanisms. For example hemodialysis accomplishes blood purification with solutes moving from high concentration to low concentration along the electrochemical gradient whether UF, as stated above, the substances travel due to a pressure gradient.

According to a duration-based classification, UF techniques can be classified as acute or isolated, intermittent or continuous (< 24 h) and slow continuous (> 24 h)[39].

With pure UF, an extracorporeal blood pump, either by suction applied to the ultrafiltrate compartment (negative pressure) or by resistance induced in the venous line (positive pressure) transfers the blood through the filter where the UF process is achieved.

Advantages of pure UF include the avoidance of arterial puncture, short exposure to systemic anticoagulation and, furthermore, it does not require specialized dialysis personnel[40].

Using an appropriate UF rate allows the extracellular fluid to gradually fill the removed intravascular space, thus keeping the volume constant; this effect differs UF from diuretics which remove intravascular volume without causing adequate filling from the extravascular space, the main site of congestion in patients with HF.

On the other hand, if the UF rate is too high, the rate by which the intravascular volume is removed exceeds the reabsorption of fluid from the interstitium into the vascular space, thus losing the real benefit of using UF.

Therefore, to obtain a real benefit from UF, the challenge is to find the correct rate of decongestion while maintaining an adequate circulating blood volume[41].

PROS AND CONS OF DIURETIC THERAPY *VS* UF

With the usage of loop diuretics, the reduction of net body water is achieved through the removal of hypotonic urine whereas UF determines the production of an iso osmotic and isonatremic diuresis. Thus, for any amount of fluid withdrawn, the net quantity of sodium removed is greater with UF than with diuretic agents.

The use of loop diuretics, moreover, causes also an inhibition of sodium chloride uptake in the macula densa thus enhancing the RAAS system activation.

On the other hand, UF through iso-osmotic and isonatremic diuresis maintains the same uptake of sodium chloride from the macula densa, avoiding RAAS system activation.

Thereby, the prolonged use of loop diuretics increases water and sodium retention in the proximal tubule with subsequent reduction of net sodium delivering in the loop of Henle decreasing the efficacy of loop diuretics to relieve the congestion.

The final goal of the ultrafiltrative process determines an euvolemic state which is obtained by withdrawing intravascular volume which is equal in size to that reabsorbed from the extracellular space [41].

Compared with standard intravenous diuretic therapy UF, by reduction of neurohormonal pathways, also improve functional capacity in patients with HF.

As explained in the study of Agostoni *et al*[42], UF unequivocally improved the functional performance of patients with HF. Cardiopulmonary exercise test obtained after 4 d shows higher values of peak VO2 and better VD/VT ratio in UF patients compared with standard diuretic therapy. The authors suggest that favorable influences of UF on the functional capacity are related to the protective role of vasopressin and atrial peptides during and after UF that allows a more “physiological" fluid metabolism and lung decongestion in patient with HF. The study also demonstrated that UF was a more powerful stimulus than loop diuretics on the release of norepinephrine, with much less effect on the RAAS system[42]. In Table 1 we highlighted main differences of using UF or diuretics.

EVIDENCES ABOUT THE USE OF UF IN HF FROM RCTS

The first two randomized clinical trial (RCT) in which an UF-based decongestion was compared to a diuretic-based approach have been the Relief for Acutely Fluid-Overloaded Patients With

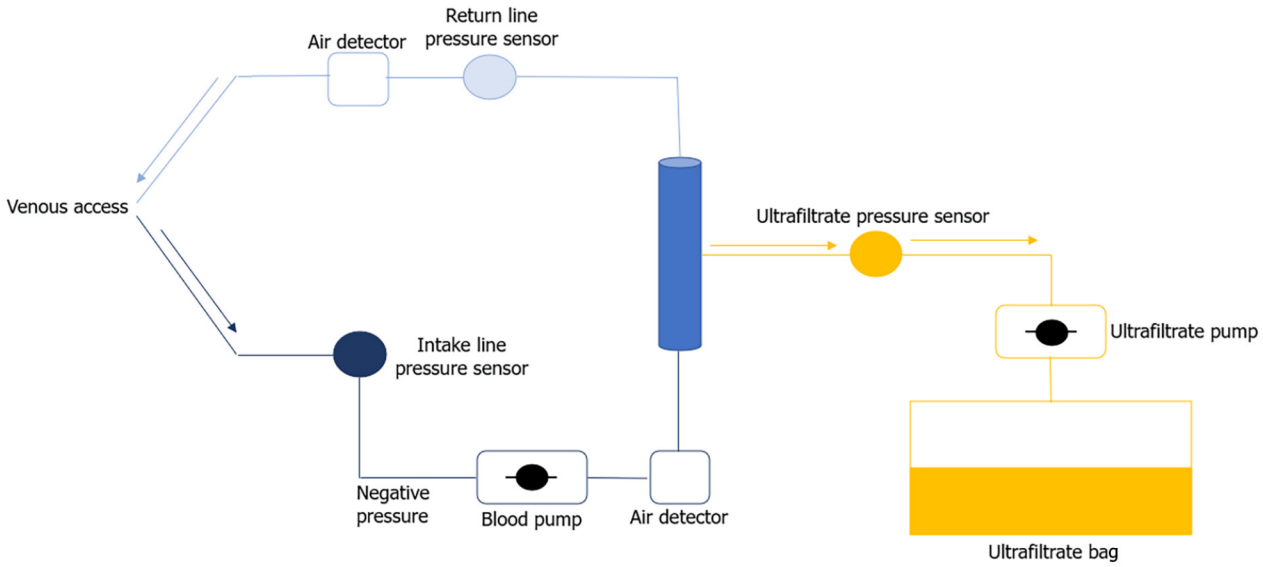

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Figure 2 A schematic representation of the ultrafiltrative process.

Decompensated Congestive Heart Failure (RAPID-CHF) and the Use of Nitroprusside in Left Ventricular Dysfunction and Obstructive Aortic Valve Disease (UNLOAD) trial[43,44].

In the RAPID-CHF, authors demonstrated the feasibility and the potential beneficial effects of UF (with Aquadex system) *vs* usual care among patients admitted to the hospital for an acute decompensation of congestive HF (20 UF, 20 usual care). These patients received a single, 8-h course of UF with fluid removal rates determined by the attending physician (to a maximum of 500 cc/h), whereas usual care patients were treated with diuretics according to the guidelines. Weight loss after 24 h from enrollment, used as primary end-point, was greater in the UF group although did not reach a statistical significance. This trial also highlighted that at 1-d and 30-d follow-up patients had a sustained and more significant symptoms relief (dyspnea) compared to the usual care. Furthermore, there were no differences between groups in terms of hemodynamic parameters (*e.g.*, blood pressure, heart rate) and adverse events.

However, the authors concluded that the small sample size (n = 40) reduced the significance of this study and did not allow to draw definitive conclusions about the potential beneficial role of UF in this subset of patients.

The investigators of the UNLOAD trial compared early UF strategy (at 24 h from hospitalization) *vs* diuretics in a population of 100 patients admitted with acutely decompensated HF in a prospective, randomized, multicenter trial. In the UF group, fluid was removed at an average fixed rate of 241 mL/h for 12 h. In the standard-care group, average daily diuretic dose of intravenous furosemide or equivalent was 181 mg during the 48 h after randomization. The study demonstrated a clear trend of each outcome in favor of UF; weight loss (primary endpoint), dyspnea improvement and net fluid loss assessed at 48 h from enrollment resulted statistically significant (P = 0.001) in the UF arm of the study as compared to diuretics arm. Furthermore, the UF group had fewer patients re-hospitalized for HF at 90 d [16 of 89 (18%) *vs* 28 of 87 (32%), P = 0.037].

One of the main limits of both the RAPID-CHF and UNLOAD trial was to not include a comprehensive assessment of hemodynamic parameters during the study.

Giglioli *et al*[45], in their ULTRADISCO trial performed a standardized evaluation of hemodynamic status obtained using Pressure Recording Analytical Method monitoring system by radial artery cannulation. Stroke volume indexed, cardiac index, cardiac power output, systemic vascular resistance was measured during hospitalization, at discharge, and at 1 and 3-mo follow-up among patients with acute decompensated HF (ADHF) treated with UF (using PRISMA system) *vs* conventional diuretics strategy. As a result, authors demonstrated that UF benefits can go beyond the net fluid loss and clinical improvement by significantly ameliorating hemodynamic status[45].

A different kind of population was target of the CARRESS-HF trial. In this study Bart *et al*[46] compared UF with a diuretic-based stepped pharmacologic therapy in patients hospitalized with ADHF with signs of congestion and worsening renal function (defined as an increase in the serum creatinine level of at least 0.3 mg per deciliter between 12 wk before and 10 d after the index admission for HF.) Ultrafiltration was performed at a fixed fluid-removal rate of 200 mL per hour. Both the primary endpoints (weight loss and serum creatinine variation) and secondary endpoints (clinical and laboratoristic) resulted statistically not significant. This trial also showed more adverse events in the UF arm such as bleeding, catheter thrombosis and advanced kidney failure. The reasons of these results remain

still unclear although it is possible that the patients involved are not the subpopulation in which UF achieve its potential beneficial effect[46].

In the CUORE trial, investigators randomized highly selected patients with severe systolic congestive HF to UF (using Dedyca system) or standard therapy. Those patients randomized to UF had a significantly lower frequency of rehospitalization for congestive HF than control subjects and this result was maintained for up to 1 year. Furthermore, the overall reduction in rehospitalizations was linked to more significant maintenance of a body weight, renal function and lower diuretic dose in the first 6 mo after discharge[47].

The AVOID-HF trial, in contrast with the CARRESS-HF trial, remains faithful to the findings of other studies mentioned above in which UF is beneficial when applied early during the episode of HF decompensation. The AVOID-HF has the largest sample size with a total of 224 patients randomized to UF arm (using Aquadex system) or standard diuretic therapy and has a predefined decongestion dose adjustment protocol. The trial was interrupted prematurely for slow enrollment rate. Despite only one third of the sample size was achieved from the investigators, this trial showed a trend toward reduction in rehospitalization for HF in the first 90-d of discharge[48].

Lastly, Hu *et al*[49], in their single center experience trial has demonstrated that early UF effectively and safely reduces volume overload in patients with ADHF. Patient were enrolled in the first 24 h of admission randomlyassigned into early UF (n = 40) or torasemide plus tolvaptan (n = 60) groups. Criteria of inclusion were acutely decompensated HF patients of age more than 18 years old and who had 1 or more sign of congestion (lung rales on auscultation, chest X ray documenting pulmonary congestion, congestive hepatomegaly and/or ascites, jugular venous pulse > 10 cm; lower limb edema, B-type NP > 400 pg/mL). Primary and secondary efficacy endpoint were increase in urine output, weight loss, reduction of dyspnea and brain natriuretic peptide; each endpoint reached statistical significance[49].

In conclusion, Table 2 summarize the different RCTs designs and outcomes.

PATIENT SELECTION CRITERIA ACCORDING TO THE LITERATURE

Given current data, it has not been yet clearly defined which subpopulation of patients suffering from acute HF refractory to diuretic therapy can benefit from UF. The conflicting results from UF studies highlight that patient selection and fluid removal targets are not completely understood.

Heterogeneity of HF patients (*e.g.*, baseline clinical characteristics, hemodynamic profile, severity of renal functional impairment), the timing and the UF protocols used in the trials contributed to these inconsistent results.

As mentioned, guidelines recommend this therapeutic option in patients with a lack of hemodynamic and laboratory response despite maximal diuretic therapy[30,31]. Unfortunately, data regarding which patients may benefit the most from this strategy are scarce.

However, despite the conflicting results of the RCTs, we can still assume some broad indications from them. According to CARRESS-HF, UF may not be useful among patients with ADHF and worsening renal function[46]. Furthermore, in contrast with all other trials, the median time from the index hospital admission (the admission qualifying the patient for enrollment in the study) to randomization was 34 h. This data reinforce the belief that a more effective UF process could be related to an earlier beginning of treatment.

From some of the trials that demonstrated an effectiveness of UF, we can suggest how continuous, or at least frequent, assessment of hemodynamic stability and fluid overload are essential prerogatives before and during the treatment[45,48].

Baseline clinical characteristics of the patient and protocol used in these trials suggest in which clinical setting UF may be used.

KNOWLEDGE GAPS, FUTURE DIRECTIONS AND ONGOING CLINICAL RESEARCH

Ultrafiltration has been principally used in decompensated HF patients as an escalation after diuretic failure or in the presence of cardiorenal syndrome. Earlier utilization of UF can expedite and maintain the compensation of acute HF by simultaneously reducing volume overload without causing intravascular volume depletion and re-establishing acid base and electrolyte balance. Despite the crucial need of alternatives to diuretics-based decongestive strategy there are still several gaps of knowledge about the correct use of UF. What clearly emerges from the literature is the lack of strong evidences able to support the routine use of UF as first and early step of treatment whereas the overall potential and beneficial effect remains clear.

To draw definitive conclusions, we need more data comings from new RCTs. At the moment, REVERSE-HF, a multicenter randomized controlled trial, is ongoing across the United States.

Table 2 Overview of most relevant randomized controlled trials on ultrafiltration-based decongestive therapy

RCTs	Target population	UF device	Primary and secondary endpoint	Results
RAPID-CHF (2005)	ADHF, *n* = 40	Aquadex system, 8-h course	Weight loss at 24 h of treatment (Primary endpoint); Volume removal after 24 h	Weight reduction resulted not statistically significant (P = 0.24); Volume removal was significantly more in UF arm (P < 0.001)
UNLOAD (2007)	ADHF, *n* = 200	Aquadex System, Mean fluid removal rate 241 mL/h	Weight loss at 48 h; Dyspnea score at 48 h	Weight loss resulted significantly increased in UF arm (P < 0.001), whereas there were no differences between groups in Dyspnea score (P = 0.588)
ULTRADISCO (2011)	ADHF, *n* = 30	PRISMA, treatment duration 46 h	Changes in hemodynamics assessed using PRAM: SVi, CI, CPO, SVR were measured during hospitalization, at discharge, and at 1 and 3-mo follow-up	UF arm as compare to standard care had a significant improvement of global hemodynamic status
CARRESS-HF (2012)	ADHF, *n* = 188; Recent increase in serum creatinin >/= 0.3 mg/dL	Aquadex System at a fixed rate of 200 mL/h	Bivariate changes in sCr and change in weight 96 h after randomization	
CUORE (2014)	ADHF, LVEF </=40%, *n* = 56	Dedyca system	HF rehospitalization at 1 yr	UF arm has a significant lower endpoint incidence (P = 0.002)
AVOID-HF (2016)	ADHF, *n* = 224	Aquadex system at an ajdusted rate on a per protocol established basis	Time to first HF event (HF rehospitalization or unscheduled outpatient or emergency treatment with intravenous loop diuretic agents or UF) within 90 days of hospital discharge	30-d HF rehospitalizations: 11 of 2876 (UF arm) *vs* 24 of 2882 (diuretics arm), P = 0.06
Hu *et al*[49], 2021	ADHF, *n* = 100	FQ-16 type HF ultrafiltration dehydration device (Beijing Hartcare Medical Technology Co., Ltd)	Weight loss and an increase in urine output on days 4 and 8 of treatment; Secondary outcome evaluated: BNP, NYHA class, IVC collapse index, JVP	Early ultrafiltration group had a significantly greater weight loss (P < 0.001) than the torasemide + tolvaptan group and urine increase (P < 0.001); Secondary outcomes that were followed up demonstated a clear trend towards benefits of UF as compared to diuretics arm

ADHF: Acutely decompensated heart failure; BNP: Brain natriuretic peptide; CI: Cardiac index; CPO: Cardiac power output; IVC: Inferior vena cava; JVP: Jugular venous pressure; HF: Heart failure; NYHA: New York Heart association; PRAM: Pressure Recording Analytical Method; sCr: Serum creatinine; SVi: Stroke volume indexed; SVR: Systemic vascular resistance; UF: Ultrafiltration; RCT: Randomized clinical trial.

An important target of decongestive therapies to achieve is the so-called dry weight; however, the best way to assess fluid status and dry weight is still a matter of debate.

POCUS can, potentially, be a helpful tool for a quick and objective fluid status assessment. There are several echographic markers of the high pressures associated with congestive process, as described above, which have been proposed[50].

However, there is still a paucity of combined POCUS scoring systems able to predict adverse outcomes of patients with clinical and laboratoristic signs of congestion. One of the proposed scoring systems is Venous Excess Ultrasound grading system of the severity of venous congestion[51].

Bioelectrical impedance (BIA) is, also, an attractive non-invasive method for assessing the total body water. Measurements of bioimpedance vector require 2 pairs of electrodes to be placed on the wrist and ankles. This method, potentially, could help the physician to guide the reduction of patient's fluid overload as showed in some trials[52].

Several authors have investigated if an objective tool such as BIA is better than clinical findings for guiding UF in hemodialysis patients. As a result of several RCTs, BIA-based interventions in hemodialysis patients for correction of overhydration have little to no effect on all-cause mortality, whereas BIA improved systolic blood pressure control. These results should be interpreted with caution as the size and power of the studies are low. Further studies, larger or with a longer follow-up period, should be performed to better describe the effect of BIA-based strategies on survival[53].

In a study by Hanna *et al*[54], they proposed that a protocol driven-UF with invasive PCWP as hemodynamic parameter can guide the physician for a safe and effective interruption of ultrafiltrative system, reaching the goal of sustained value </= 18 mmHg for more than 4 h.

The use of biomarkers able to show acute kidney injury can help physician to assess fluid status and guide decongestion. At the state of art, serum creatinine is the sole biomarker used in daily practice to guide fluid removal. However, serum creatinine can be elevated also in the context of volume depletion without acute tubular damage. Conversely, this parameter can be normal in documented tubular injury due to the delayed achievement of detectable changes of this analyte. It is therefore evident that we need to undercover new useful biomarkers able to be more specific for kidney damage. Neutrophil gelatinase-associated lipocalin (NGAL) attracts as a newly more specific biomarker of acute kidney

injury; NGAL is not elevated in case of volume depletion as serum creatinine. In vitro studies found other genes expressed only after brief dose of ischemia as kidney injury molecule-1, tissue inhibitor of metalloproteinase-1, and clusterin, although none of these genes were expressed after volume depletion, despite the rise in serum creatinine in both models[55].

CONCLUSION

In conclusion, ultrafiltration represents an attractive alternative to pharmacologic therapy. More long-term data about safety, incidence of rehospitalization for HF and cost-effectiveness are crucial to definitely allocate this treatment also as a main option. Furthermore, we need more comprehensive and non-invasive tools to guide physicians in the fluid status management of congested patients.

FOOTNOTES

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