

Extracorporeal Ultrafiltration for Acute Heart Failure

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Keywords

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Abstract

Acute decompensated heart failure (ADHF) has the highest rate of hospital readmission among all medical conditions and portends a significant financial burden on healthcare systems worldwide. Hospitalization for ADHF is primarily driven by congestion, with intravenous loop diuretics representing the cornerstone of therapy. However, it is well described that a significant subset of patients is discharged with residual fluid overload. While the cause of the incomplete decongestion is multifactorial, the development of diuretic resistance is a well-characterized contributing factor with consequent poor outcomes. Moreover, the therapeutic response to diuretics is known to lack predictability. Extracorporeal ultrafiltration (a mechanical pump-driven therapy) has emerged as an option to overcome shortcomings of the diuretics. It allows clinicians to customize the volume and the rate of fluid removal to the needs and clinical characteristics of the patients. The results of the currently available studies indicate that this therapy is associated with more efficient fluid and sodium removal compared to medical therapy, hence leading to reduction in the rate of readmissions and a potential salutary impact on the financial bur-

den associated with the care of these patients. While isolated ultrafiltration can be performed by conventional machines used for renal replacement therapy, the advent of simplified, portable, and user-friendly devices that are specifically designed for extracorporeal ultrafiltration therapy has further enhanced the interest in this therapeutic modality and increased the potential for its more widespread use. Further, development in this direction through device miniaturization may extend the horizons of indications and the applicability of this therapy even in the ambulatory settings.

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Background

Heart failure represents a major public healthcare problem due to its high prevalence, morbidity, mortality, and significant financial burden on the healthcare system. Approximately 6.5 million adults in the USA have heart failure, and one in eight deaths includes it as a contributing cause of mortality [1]. Nearly, 40–45% of patients who develop heart failure die within 5 years of diagnosis [1]. The course of chronic heart failure is highlighted by episodes of exacerbation. Acute decompensated heart failure remains among the leading causes of hospital admission in older patients exceeding one million in both the USA and Europe with more than one million hospitalizations

annually [2]. It has the highest rehospitalization rate among all medical conditions; one in 4 patients (24%) are readmitted within 30 days, and one in 2 patients (50%) are readmitted within 6 months [2, 3]. The annual cost of the care for patients with heart failure is estimated at 60 billion dollars in the USA with expenses related to the hospital care accounting for almost 70 percent of the total expenditure [4]. As the population ages, healthcare expenditures are expected to increase substantially [5]. Congestion is the primary reason for hospitalization of patients with heart failure [2, 6]. Venous congestion can cause endothelial activation and upregulation of inflammatory mediators with systemic effects that include impairment of renal function, intestinal villi ischemia, and hepatic dysfunction [7]. Removal of excess fluid constitutes a major goal in the management of patients with ADHF.

Pharmacological Decongestion

Loop diuretics remain the cornerstone of therapy for fluid overload in patients with heart failure due to their favorable diuretic profile of achieving urinary sodium excretion without excessive potassium wasting at lower doses. While effective early in the course of heart failure, the efficacy of diuretics gradually decreases as the disease progresses in a significance subset of patients [8]. As such, diuretic resistance (i.e., persistent fluid overload despite an adequate and escalating dose of loop diuretics) has been a well-known challenge in the care of these patients, and not surprisingly is tied to worse prognosis [8, 9]. Impaired intestinal absorption, decreased renal blood flow, nephron remodeling, renal venous congestion, and neurohormonal activation are among the underlying pathophysiological mechanisms leading to reduced responsiveness of these patients to diuretics [9]. The clinical hallmarks of loop diuretic resistance are inadequate relief of congestion, increased risk of in-hospital worsening of heart failure, and a significant increase in rehospitalization rates [10].

Sequential blockade of the renal tubules through combination of diuretics with different mechanisms of action, replacing oral agents by intravenous medications during admission to the hospital, infusion of intravenous diuretics instead of bolus administration, and gradual escalation of the dose of the diuretics are among the common strategies that clinicians have used for decades to overcome apparent diuretic resistance [11, 12]. Several observational studies have shown poor outcomes with use of high-dose loop diuretics which has been attributed to

stimulation of renin-angiotensin-aldosterone and sympathetic nervous systems [13–15]. Post hoc analysis of ADHERE database showed that patients receiving high dose of diuretics had poor outcomes in comparison to patients receiving lower doses [14]. Similar results were seen with ESCAPE trial in which high-dose diuretics increased mortality especially when the daily dose of furosemide exceeded 300 mg [15]. These studies could be confounded by the fact that patients with more severe disease are likely to receive higher doses of diuretics; the diuretic dose may possibly be a marker of severity of the disease rather than a cause for adverse outcomes.

Patients with ADHF frequently experience suboptimal decongestion, and nearly 50% of them leave the hospital with inadequate or minimal weight loss [16]. Therefore, in recent years, there has been a renewed interest in identifying the pathways underlying diuretic resistance. Moreover, there has been a proposal for shifting of the patient's monitoring of responsiveness to diuretics from conventional metrics, such as weight change and urine output, to measurement of urinary excretion of sodium. Some authors have proposed algorithms for diuretic therapy in patients with ADHF that are based on measurements of spot urine sodium after administration of a loop diuretic [17]. However, it has been shown that natriuretic response is highly variable in patients who are admitted to the hospital for ADHF [18] and emerging reports have challenged the supposition that urinary sodium concentration remains constant throughout the course of hospitalization [19]. In parallel, there have been attempts to develop clinical tools and calculators to predict the patient's response to diuretics and guide the dosing in order to increase the efficiency of these agents and overcome the challenge of diuretic resistance [20, 21]. While these methods do seem promising, it should be noted that they are at their infancy, and the investigations are mostly single-center pilot studies performed in academic centers primarily as proof of concept. Therefore, it remains unclear whether they can be applicable to real-time clinical practice of centers with limited resources where a significant number of such patients are being admitted. Table 1 summarizes some of the proposed shortcomings of diuretic use in the setting of heart failure.

Ultrafiltration Process

Ultrafiltration is an extracorporeal process in which plasma water devoid of cells and colloids is forced by hydrostatic pressure across a biosynthetic, semipermeable

Table 1. Potential shortcomings of diuretic use in treatment of heart failure

Direct activation of renin-angiotensin-aldosterone system
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)
Nonrenal adverse effects (e.g., ototoxicity and hypersensitivity)

Adapted with permission from reference 22.

filter, resulting in the removal of water, electrolytes, small solutes (e.g., water-soluble vitamins). During this process, blood exits the body through a venous catheter in order to reach the hemofilter. Hydrostatic pressure is exerted across the filter (i.e., a semipermeable membrane) and results in the production of ultrafiltrate which is basically composed of water and smaller solutes such as sodium and potassium that have been dragged out along with the water. The concentration of these solutes will be similar between the ultrafiltrate and serum, hence lack of any impact of ultrafiltration on the serum levels of these solutes (i.e., the ultrafiltrate produced is almost isotonic compared with the plasma). The ultrafiltration rate is adjusted by modifying the positive pressure that is applied to the blood side of the membrane or the negative pressure that is exerted on the ultrafiltrate side. This rate will be determined by the amount of fluid that needs to be extracted as well as clinical characteristics of the patient such as hemodynamics status. The hemoconcentrated blood is then returned back to the patient via the venous access. The progressive reduction in intravascular volume and concomitant increase in the oncotic pressure of serum will lead to shift of fluid from interstitial to replenish intravascular compartment. Therefore, while fluid removal in ultrafiltration is directly from intravascular sector, it will ultimately lead to removal of excess fluid from extravascular and interstitial compartments. It is important to note that this process relies on adequate shift of fluid from interstitium to refill plasma water; hence, the importance of carefully setting the rate of ultrafiltration in order to avoid overzealous fluid extraction with potential adverse impact on the hemodynamics or perfusion of vital organs such as the kidney. The process of ultrafiltration is fundamentally different from hemodialysis in that there is no dialysate used in this form of therapy, hence

Table 2. Proposed advantages of ultrafiltration in treatment of heart failure

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 heart failure-related rehospitalizations
Decreased hospital length of stay
Availability of dedicated ultrafiltration 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. Adapted with permission from reference 22.

lack of diffusion of solutes across the hemofilter (and therefore no clearance of solutes) which is the basis of hemodialysis modality.

Although isolated ultrafiltration can be performed with conventional hemodialysis machines to solely extract fluid without providing clearance, there have been dedicated devices marketed exclusively for management of fluid overload. These devices with newer technology are simplified user-friendly machines that have the advantages of small size, portability, blood flow rates of as low as 40 mL/min (as compared to 300–450 mL/min in conventional dialysis machines), and an extracorporeal blood volume of less than 50 mL. They can provide ultrafiltration rates within a large spectrum (0–500 mL/h), do not mandate admission to intensive care unit, and have been marketed with the ability of even using peripheral veins [22]. Table 2 summarizes some of the proposed advantages of ultrafiltration therapy in the setting of heart failure.

Clinical Trials

Earlier trials of ultrafiltration for heart failure have been instrumental as proof of concept for feasibility of this therapeutic option and have been quite successful in generating the interest for consideration of mechanical

fluid extraction as an alternative to medical therapy. However, not all their results might be reproducible in the current era due to the fact that both medical management and the technology and practice of extracorporeal therapy have changed dramatically over the last two decades. In one of the largest earlier studies, Canaud et al. [23] used slow ultrafiltration therapy (continuous or daily) in 52 patients with severe congestive heart failure and showed that the patients could tolerate significant fluid removal (i.e., an average weight loss of 9.2 kg). These studies also suggested that the salutary effects of ultrafiltration in this setting might be sustainable beyond the duration of therapy. In a study of 36 patients with heart failure, Agostoni et al. [24] reported an improvement in several respiratory parameters (e.g., tidal volume and peak exercise ventilation) that lasted over the next 6 months following one single session of ultrafiltration. In a similar study, those patients with heart failure who underwent one session of ultrafiltration showed improvement in cardiorespiratory parameters (e.g., exercise tolerance time) that persisted at 1- and 3-month follow-up assessments; these effects were not observed in the control group [25].

Following a clinical study in 2003 where the feasibility of using peripherally inserted venous catheters for fluid overloaded patients with heart failure was successfully tested [26], Costanzo et al. [27] performed a study of ultrafiltration on patients with ADHF who also presented with diuretic resistance or renal dysfunction. They reported favorable results with successful decongestion, significant shorter length of stay, and lower readmission rates. In 2007, the long expected first large-scale randomized controlled trial in this field was published. In Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial, patients who were treated with ultrafiltration experienced significantly greater weight loss (i.e., decongestion) compared to those who received diuretics [28]. Interestingly, the ultrafiltration group demonstrated a greater freedom from rehospitalization during the 3-month follow-up period as well; ultrafiltration was associated with >50% reduction in the risk of rehospitalization for ADHF. In line with previous studies suggesting that the beneficial effects of ultrafiltration are sustainable, a secondary analysis of the UNLOAD trial found that, with comparable fluid volume removal for ultrafiltration and diuretic infusion, still fewer heart failure rehospitalization equivalents occurred with ultrafiltration [29]. In 2012, a second large randomized controlled trial was published. In contrast to UNLOAD, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CAR-

RESS-HF) trial included patients with ADHF who also presented with cardiorenal syndrome and persistent congestion despite conventional treatment [30]. The patients were randomized to receive either an algorithm-based pharmacological regimen or ultrafiltration as a rescue therapy. Surprisingly, not only did patients in the ultrafiltration group fail to have greater weight loss, but they also presented with an increase in serum creatinine level. The main concern about the design of this trial was that while dosing of the diuretics was adjusted in the pharmacological therapy arm based on patients' therapeutic response, the rate of ultrafiltration was delivered uniformly at 200 mL/h. We have previously discussed the importance of customization of ultrafiltration rate based on plasma refill and patient's clinical characteristics to avoid adverse effects [31]. Nevertheless, the investigators did not observe a difference in the mortality of the two groups during the 2-month follow-up [30]. Several years later, a per-protocol analysis of CARRESS-HF (i.e., inclusion only of subjects who received their randomized treatment) found that ultrafiltration was indeed associated with higher cumulative fluid loss, net fluid loss, and relative reduction in weight compared to stepped, urine output-guided pharmacological therapy [32]. Regarding the increase in serum creatinine that was observed in the ultrafiltration arm, accumulating evidence suggests that transient increases in serum creatinine may not represent the renal injury and instead signify a hemodynamically driven reduction in glomerular filtration rate, indicative of effective decongestion with improved outcomes [33, 34].

The negative results of CARRESS-HF contrasted those of UNLOAD and several previous uncontrolled trials. Due to the differences in the design and delivery of the interventions, there was a need for a fair comparison between a protocolized diuretic regimen with a well-done algorithm-based ultrafiltration therapy. The Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial was designed to address this knowledge gap [35]. It compared early adjustable ultrafiltration therapy with a carefully designed medical treatment protocol that had similarities with the algorithm used in the CARRESS-HF. The total and net fluid losses were again found to be greater in the ultrafiltration group than in the diuretic arm without an adverse impact on renal function. The patients in the ultrafiltration arm showed a nonsignificant trend toward better outcomes such as higher estimated number of days to the first HF event within 3 months after discharge.

To consolidate data across several studies, a number of meta-analyses have been performed. Jain et al. [36]

Table 3. Selected studies of ultrafiltration in heart failure

	UNLOAD [28]	ULTRA DISCO [38]	Hanna et al., [39]	CARRESS-HF [30]	CUORE [40]	AVOID-HF [35]
Year of publication	2007	2011	2012	2012	2014	2016
Centers, <i>n</i>	28	1	1	22	2	30
Patients, <i>n</i>	200 (100 UF, 100 PT)	30 (15 UF, 15 PT)	36 (17 UF, 19 PT)	188 (94 UF, 94 PT)	56 (27 UF, 29 PT)	224 (110 UF, 114 PT)
Study design and protocol	RCT, single session early UF therapy for ADHF (within 24 h)	RCT, slow continuous UF, hemodynamic changes were monitored by pressure recording analytical method	RCT, slow continuous UF for ADHF, patients were randomized within two strata based on baseline GFR	RCT, rescue therapy for patients with both ADHF and WRF	RCT, one or two early UF treatments for ADHF (within 24 h)	RCT, single session early UF therapy for ADHF (within 24 h)
Primary endpoint	Weight loss and dyspnea at 48 h (efficacy), changes in renal function and hypotension (safety)	Change in clinical, biohumoral, and hemodynamic parameters	Time for PCWP to be kept at ≤ 18 mm Hg for at least 4 consecutive hours	The changes in Scr and weight at 96 h (bivariate)	Rehospitalization rate for HF at 1 year	Time to first HF event within 90 days after discharge
Ultrafiltration regimen	Duration and rate of UF flexible, maximum UF rate 500 mL/h, Average UF rate 241 mL/h for 12.3 \pm 12 h	Blood flow rate of 150 mL/h, adjustable UF rate of 100–300 mL/h	Blood flow rate of 200–300 mL/min, UF rate of 400 mL/h for 6 h and then 200 mL/h	Fixed UF rate 200 mL/h, median duration of UF 40 h, Median duration 40 h	Duration and rate of UF flexible, maximum UF rate 500 mL/h, average duration 19 \pm 10 h	Duration and rate of UF flexible, Maximum UF rate 500 mL/h, average UF rate 138 mL/h for 80 \pm 53 h
Medical therapy	Conventional pharmacologic therapy (no pre-planned algorithm)	Conventional pharmacologic therapy (no pre-planned algorithm)	Conventional pharmacologic therapy (no pre-planned algorithm)	Stepped pharmacologic therapy (algorithm-based)	Conventional pharmacologic therapy (no pre-planned algorithm)	Adjustable intravenous loop diuretics (algorithm-based)
Age, years	62 UF, 63 PT	72 UF, 66 PT	60 UF, 59 PT	69 UF, 66 PT	75 UF, 73 PT	67 UF, 67 PT
Male gender, %	70 UF, 68 PT	87 UF, 87 PT	84 UF, 76 PT	78 UF, 72 PT	81 UF, 83 PT	69 UF, 73 PT
Weight, kg	101 UF, 96 PT	74 UF, 83 PT	93 UF, 98 PT	94 UF, 106 PT	83 UF, 89 PT	110 UF, 111 PT
LVEF, %	71 UF ^a , 70 PT ^a	34 UF, 30 PT	19 UF, 18 PT	30 UF, 35 PT	32 UF, 32 PT	36 UF, 37 PT
Baseline Scr, mg/dL	1.5 UF, 1.5 PT (Scr >3 mg/dL excluded)	2.2 UF, 1.9 PT (Scr >3.0 mg/dL excluded)	55 UF, 51 PT ^b (eGFR <15 excluded)	1.9 UF, 2.09 PT (Scr >3.5 mg/dL excluded)	1.7 UF, 1.9 PT (Scr >3 mg/dL excluded)	1.5 UF, 1.6 PT (Scr \geq 3 mg/dL excluded)
Impact on renal function	No significant difference in renal function between UF and PT	No significant difference in renal function between UF and PT	No significant difference in renal function between UF and PT	Significant increase in Scr level with UF, no change in Scr for PT	Higher Scr and BUN in the PT group at 6 months, No difference in eGFR, Scr, and BUN between UF and PT at 1 year	No significant difference in eGFR, Scr, BUN, and BUN/Scr ratio during treatment and up to 90 days between UF and PT
Impact on congestion	Greater weight loss with UF, Greater net fluid loss with UF	Weight loss and total amount of fluid removal similar for both groups	Similar total volume extraction for UF and PT, Significantly higher fluid removal rate with UF	Weight loss and total amount of fluid removal similar for both groups	Weight loss similar for both groups at discharge, Lower body weight for UF at 1 year	Higher total amount of fluid removed with UF, No difference in weight loss between UF and PT
Impact of UF versus PT on readmission	Improved	NR	Similar	Improved	Improved	Improved
Follow-up, months	3	[36 h]	3	2	12	3

UF, ultrafiltration; PT, pharmacologic therapy; HF, heart failure; Scr, serum creatinine; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; NR, not reported; PCWP, pulmonary capillary wedge pressure; eGFR, estimated glomerular filtration rate; BUN, blood urea nitrogen; Scr, serum creatinine; WRF, worsening renal function; RCT, randomized controlled trial; AVOID-HF, Aquapheresis versus Intravenous Diuretics and Hospitalization for Heart Failure; CARRESS-HF, Cardiorenal Rescue Study in Acute Decompensated Heart Failure; CUORE, Continuous Ultrafiltration for Congestive Heart Failure; ULTRADISCO, Effects of Ultrafiltration versus Diuretics on Clinical, Biohumoral and Hemodynamic Variables in Patients with Decompensated Heart Failure; UNLOAD, Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure. Adapted with permission from reference 36. ^aPercentage of patients with LVEF \leq 40%. ^bEstimated glomerular filtration rate (eGFR).

pooled data from 7 randomized controlled trials of ultrafiltration including a total of 771 patients. They found that, based on the available data, ultrafiltration therapy is indeed associated with more efficient decongestion as measured by weight loss and net fluid removal compared with medical treatment. Although there were similar changes in renal function for both groups, ultrafiltration was shown to be more efficient at reducing the rate of HF rehospitalization, possibly by virtue of more efficient decongestion. There was no difference in mortality rate or incidence of adverse events. These results lend support to the previously mentioned notion that the high rate of heart failure rehospitalization could in part be related to suboptimal decongestion during index hospital admission; the therapy with better decongestive properties would lead to improved rate of readmission. It also implies that ultrafiltration could potentially have a role in reduction of heart failure-related cost as the majority of the expenditure is related to the inpatient care of these patients. In line with this observation, a recent hospital cost analysis revealed that while initial hospitalization costs are higher for patients with ADHF who receive ultrafiltration therapy, this therapeutic modality is cost-saving (by more than 14%) at 90-day timeframe due to reduction in hospital readmission days [37]. Table 3 summarizes selected studies of ultrafiltration therapy in the setting of heart failure.

Future Research

Prediction of outcomes in patients with heart failure has been a topic of much investigation. The functional decline related to repeated episodes of acute decompensation followed by partial recovery makes it challenging to reliably predict the effectiveness of the medications and devices in this setting. The heterogeneity of heart failure, with multiple etiologies, distinct phenotypes, and the presence of a multitude of comorbidities makes it unlikely for every subset of patients to benefit from population-based approaches (i.e., one-size-fits-all). Future significant improvements in clinical outcomes of patients with heart failure could be achieved when therapy is individualized and tailored to a patient's biological profile and clinical characteristics (i.e., personalized medicine). This practice can be further promoted by integrating a significant amount of biological information (e.g., genomes and proteomes) to large-scale clinical data (i.e., precision medicine), which will enable the selection of the optimal treatment option(s) for individual patients with heart

failure. There are certain concerns that need to be addressed with regard to the use of ultrafiltration therapy in this setting. Lack of protective effect on renal function, need for additional training for staff and physicians, need for anticoagulation, complications related to extracorporeal circuit (e.g., air embolism and infection), and lack of knowledge on the long-term outcomes are among the proposed limitation of this therapy [22]. Identifying the subset of patients who benefit the most from ultrafiltration therapy could be achievable using these principles. Timing of initiation and ending of therapy can also be determined through this process. Similar to other therapeutic interventions in heart failure, in order to explore the efficacy of ultrafiltration therapy using the precision medicine approach, there would be a need to use endpoints besides mortality (e.g., resolution of congestive symptoms and increase in the time interval between hospital admissions). Furthermore, advances in technology should allow development of small portable or wearable devices that, while sophisticated, are simple to use (e.g., through miniaturized filters and circuits). Ultrafiltration versus IV Diuretics in Worsening Heart Failure (REVERSE-HF) is a multicenter open-label randomized controlled trial (NCT 05318105) that is designed to compare adjustable ultrafiltration therapy with an adjustable diuretic regimen, and explore their impact on outcomes (e.g., first heart failure event and mortality).

Conclusion

Based on the findings of the available trials, ultrafiltration represents an efficacious and safe therapeutic option for selected patients with ADHF, such as those with resistance to diuretics or a history of multiple hospitalizations for congestion. This pump-driven technique of decongestion provides predictable, adjustable, and more efficient fluid removal compared to diuretics without clinically significant adverse impact on renal function. It can be considered early after admission to the hospital, and the volume and rate of fluid removal need to be customized to the clinical characteristics and specific needs of each patient (e.g., weight gain, blood pressure, and the presence of right ventricular dysfunction). It will be prudent to avoid overzealous fluid extraction in order to prevent imbalance in plasma refill rate, induce intravascular contraction, and exacerbate neurohormonal activation. While there has been no head-to-head comparison for rate or volume of fluid removal in this setting, some authors have used less aggressive fluid removal in patients

with right-sided heart failure and those with tenuous hemodynamic status [30, 35].

Due to the significant adverse impact of persistent congestion on the outcomes, in cases where the patient shows slight deterioration in renal function while still fluid overloaded, it might be reasonable to favor complete decongestion over preservation of renal function, especially if the increase in serum creatinine is not significant and urine output is preserved. With the advent of newer devices that are dedicated to ultrafiltration therapy and are user-friendly and portable, it is conceivable that the use of this modality will expand over the next few years as the data on its various practical aspects, such as optimal timing of initiation and termination of therapy, continues to emerge. Moreover, ultrafiltration therapy might prove useful in other clinical settings where active and prompt volume management is of utmost importance (e.g., post cardiac surgery, burn units, right-sided heart failure after left ventricular assist device implantation). Currently, some centers that are specialized in the care of patients with heart failure provide transition units where the patients with progressive fluid overload can be treated with intravenous diuretics without the need for admission to the hospital. If future studies confirm the safety of ultrafiltration therapy in the ambulatory setting, it can be used in transition units for efficient fluid removal and prevention of hospital admission for patients with persistent or worsening fluid overload despite treatment with diuretics. Similar to current home-based renal replacement therapies, with recent advances in telemedicine technology and simplified devices, the application of ultrafiltration can potentially expand beyond in-center therapy in the future and be safely performed by patients in the comfort of their home. Furthermore, a small wearable device

that allows ambulatory ultrafiltration to be performed slowly and continuously could eliminate clinically significant hemodynamic changes and obviate the need for spending several hours attached to a stationary ultrafiltration device.

Conflict of Interest Statement

Amir Kazory has the following potential conflicts of interest: Baxter, Inc. (Cardiology Advisory Board and consultancy fee), Nu-Wellis, Inc. (Medical Advisory Board and consultancy fee), Relypsa, Inc. (consultancy fee), and W.L.Gore Inc. (consultancy fee), Elsevier (consultancy fee). Luca Sgarabotto has no conflicts. Claudio Ronco in the last 3 years has been consulting or part of advisory boards for Astute, Baxter, Biomerieux, B.Braun, Cytosorbents, ESTOR, FMC, GE, Jafron, Medtronic, and Toray.

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Author Contributions

Amir Kazory: conceptualization, gathering the data, and preparing the draft. Luca Sgarabotto: critical review of the manuscript. Claudio Ronco: conceptualization and critical review of the manuscript.

Data Availability Statement

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