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Chapter 5

Effectiveness of Ultrafiltration in Patients with Congestive Heart Failure

Luai Alhazmi, Abdulelah Nuqali, Ankush Moza and Mujeeb Sheikh

Additional information is available at the end of the chapter

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Abstract

Among all cardiac diseases, congestive heart failure (CHF) is the leading cause of patient rehospitalization. Fluid overload and lung congestion are the major reasons for these recurrent admissions. This disease can be associated with worsening renal function, a phenomenon called cardiorenal syndrome (CRS), which is challenging to manage. Conventional diuretic therapy of both CRS and diuretic resistance has offered limited efficacy. Compared with conventional therapy, hemodiafiltration (HDF) has shown promising results for fluid removal in some clinical trials, with inconclusive effects on all-cause mortality and rehospitalizations. Nonetheless, the results are inconsistent because of the high heterogeneity among these studies. In this chapter, we shed light on the role of different methods of ultrafiltration, including peritoneal ultrafiltration, sustained slow efficiency dialysis, and HDF, in the management of CHF, and review the current literature.

Keywords: congestive heart failure, cardiorenal syndrome, peritoneal ultrafiltration, sustained low efficiency dialysis, hemodiafiltration

1. Introduction

Congestive heart failure (CHF), sometimes called chronic heart failure or simply heart failure, is a disease that affects a patient's everyday life and can have deleterious effects on both physical and mental well-being [1–3]. Patients with CHF have a worse health-related quality of life than those with many other chronic diseases, such as chronic obstructive pulmonary disease, hypertension, diabetes mellitus, and myocardial infarction [3, 4]. Moreover, rehospitaliza-

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tions are a major concern among these patients, their families, and their health service providers. CHF causes the highest rehospitalization rate among all chronic diseases, reaching up to 27% [5]. Patients with CHF have a poor prognosis, with a 1-year survival rate that is comparable or worse than that for common neoplasms such as prostatic or breast malignancies. Stewart et al. showed that the median survival time for patients with CHF was 16 months with 25% 5-year survival rate [6, 7]. Despite all advances in the management of CHF, it is still the leading cause of mortality among cardiac diseases [8, 9]. Fluid overload and lung congestion are the most recurrent cause of admissions in these patients [10]. Almost 50% of them are discharged with residual congestion, and most rehospitalizations occur in patients who are diuretic resistant [11]. Diuretic resistance, in which patients with CHF have reduced diuresis and natriuresis in response to diuretics, causes higher mortality and rehospitalizations [10, 12, 13]. CHF is also associated with cardiorenal syndrome (CRS), a condition in which renal function worsens and is challenging to manage [14]. Conventional diuretic therapy of both CRS and diuretic resistance has shown limited efficacy with no robust data on efficacy in terms of well-designed randomized clinical controlled trials [15, 16]. However, hemodiafiltration (HDF), isotonic fluid replacement through positive hydrostatic pressure, has recently emerged as an alternative or last resort for these complex patients. The aim of this physiological approach is to decrease neurohumoral activation, which in turn curbs the vicious cycle leading to cardiac and renal insult [17, 18]. Some promising results have been reported in initial studies, but the data conflict and are inconclusive. As a result, no clinical guidelines to date have adopted HDF as an alternative to diuretic therapy [10, 19–22].

2. Diuretic resistance and CRS syndrome

No specified definition is available for diuretic resistance, as it is the outcome of treatment and not a pathological condition in itself. The efficacy of loop diuretics can be evaluated as a measure of urine output, change in weight, and balance in net fluid [23]. Patients unable to meet their needs for decongestion despite high doses of loop diuretics are generally labeled as diuretic resistant. Some current studies have reported the efficacy of diuretics in terms of clinical outcomes in patients with CHF [24–31]. Although these studies used different methods and metrics, the outcomes were similar in all: patients with diuretic resistance showed poor outcomes compared with those without diuretic resistance. Even after correcting for glomerular filtration rate (GFR), a strong correlation between worse clinical results and diuretic resistance was observed, showing that the efficacy of diuretics and the GFR each have a different impact on clinical outcomes. GFR is a good indicator of the kidney's clearance ability. When this rate is normal, the renal tubules are able to maintain homeostasis of electrolytes and euvolemia. Even if the GFR is reduced to up to 20 mL/min, usually 28.8 L of fluid is filtered, and sodium excretion is about 4000 mEq. The metrics used in current studies for diuretic efficacy are indirectly related to the effectiveness of loop diuretics for sodium excretion. Consequently, these metrics indicate a better prognosis than does the GFR in terms of the kidneys achieving euvolemia.

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Several studies that used different metrics tried to establish a correlation between efficacy of diuretics and heart failure-related clinical outcomes. In the case of patients having reduced diuretic efficacy, Testani et al. [24] found high mortality rates even after correcting for diuretic dose and fluid output. Valente et al. [25] and Voors et al. [31] observed increased death and rehospitalization rates associated with diuretic resistance in heart failure at 60 days, whereas Ter Maaten et al. [28] reported similar outcomes at 30-day follow-up. After correcting for the GFR, Verbrugge et al. [29] and Singh et al. [26] reported higher death and rehospitalization rates related to diuretic resistance.

On the contrary, CRS is a condition that becomes apparent from a decrease in the GFR and acts as a barrier to the treatment of CHF by limiting the renal function [32]. At first, a decrease in blood flow in the kidney was considered to cause a low GFR, but recently a number of studies have shown that cardiorenal interactions have several complex mechanisms, some of which may be reversible. In a commonly used classification given by Ronco and colleagues [33], CRS is grouped into four types: type 1 is characterized by acute heart failure, leading to acute kidney injury; type 2 involves chronic cardiac impairment such as CHF, resulting in chronic kidney disease; type 3 is a result of primary kidney function impairments, resulting in acute cardiac impairment that may become evident as heart failure; and type 4 involves chronic cardiac impairments influenced primarily by primary chronic kidney disease such as uremic cardiomyopathy. A further type 5 CRS involves systemic disorders of the chronic or acute type such as sepsis; diabetes causes both cardiac and renal dysfunction.

Acute CRS is a reflection of worsening renal function in patients with CHF [34]. CRS is found in 25–33% of all patients with acute decompensated heart failure (ADHF) [35, 36]. Extrarenal hemodynamic changes, cellular dysregulation, neurohormonal activation, and intrarenal microvascular and oxidative stress underlie acute CRS [34, 37]. In a few cases, intravenous diuretic-mediated renal injury is responsible for worsening renal function [16, 38, 37]. Other proposed mechanisms of CRS pathophysiology include neurohumoral adaptations, reduced renal perfusions, elevated venous pressure, and dysfunction of the right ventricle [39, 40].

3. Peritoneal ultrafiltration (pUF)

In advanced stages of CHF, a decline in renal function can often be seen, consistent with type 2 CRS (CRS-2). Several therapies have been evaluated for this group of patients; however, the optimal therapy for "chronic" CRS remains elusive. It is believed that peritoneal ultrafiltration (pUF) may lead to improvement in the clinical function of these patients, with a reduction in the number of hospitalizations.

A study performed on patients without end-stage renal disease evaluated the efficacy of pUF in the treatment of chronic refractory heart failure (HF) [41]. For this evaluation, 39 consecutive patients with end-stage CHF and stable CRS-2 were given ambulatory pUF and prospectively followed for 1 year. The primary end point was all-cause hospitalization. Mortality, treatment changes, and weight changes with New York Heart Association (NYHA) functional class and quality of life were considered as the secondary end points. Compared with the control group, who received standard treatment, in the pUF group, there was a reduction in the number of

1-year hospitalization days ($p = 0.07$). However, the 1-year mortality was found to be 33% in the pUF group and 23% in the control cohort, although this result was not statistically significant. In comparison to standard medical treatment, pUF was found to significantly improve volume overload ($p < 0.05$), the NYHA functional class ($p < 0.001$), and mental health ($p < 0.05$) of the patients. Furthermore, in the pUF group, the hospitalization days for all causes, including cardiovascular incidents, were significantly reduced during the interim periods ($p < 0.05$ and $p < 0.001$, respectively).

Another study evaluated pUF in patients with severe HF that was refractory to aggressive drug therapy [42]. Treatment with pUF was considered in these patients, as they had been hospitalized at least three times in the preceding year for ADHF that had required extracorporeal UF. This study comprised 48 patients; of those, 30 received one nocturnal icodextrin exchange, 5 received two daily exchanges, and the remaining 13 received two to four sessions per week of automated peritoneal dialysis (PD). In the first year of therapy, renal function remained stable with a decline in pulmonary artery systolic pressure to 40 ± 6.09 mmHg from 45.5 ± 9.18 mmHg ($p = 0.03$). At the same time, significant improvement was noted in the NYHA functional status. Furthermore, patient hospitalizations decreased to 11 ± 17 days/patient-year from 43 ± 33 days/patient-year seen in the preceding year, which was before the onset of PUF treatment ($p < 0.001$). Thus, this study confirms the efficacy of PUF treatment in elderly patients with chronic HF.

Recently, a systematic review conducted to evaluate the efficacy of PD in patients with refractory CHF identified 21 studies from 13 countries [43]. This review comprised 673 patients and suggested that in patients with refractory CHF, PD can be an effective and safe treatment option, leading to improved heart function and weight control. It also reported that PD can reduce patient hospitalization days without any progressive worsening of renal function. The rates of PD complications such as peritonitis were also found to be acceptable.

4. Sustained low-efficiency dialysis (SLED) in patients with CHF

Sustained low-efficiency dialysis (SLED), or sustained low-efficiency daily dialysis (SLEDD), is a conventional hemodialysis that is performed over a longer period (6–12 h) of time using lower rates of blood flow (50–200 mL/min) and dialysate flow (200–400 mL/min). It is an alternative treatment in critically ill patients with affected kidney function [44–46], where fluid is removed slowly over longer time ensuring better hemodynamic stability [47]. This is in particular the case when the cost of HF/HDF is considered expensive. It combines the logistic advantages, the cost-effectiveness and the scheduling flexibility of the intermittent dialysis, and the hemodynamic stability of continuous renal replacement therapy with fewer side effects during the fluid removal [48]. There is still a limited clinical data in the literature on the effectiveness of SLED in patients with CHF. However, Iorio et al.'s experience suggested that SLED is an alternative treatment for acute dialysis in patients with diuretic resistant systolic CHF [49]. Violi et al. mentioned that the SLED as an alternative treatment is the most indicated in NYHA class IV CHF [50].

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5. Hemodiafiltration in a nutshell

Dialysis refers to diffusive clearance. During dialysis, low-molecular weight solutes such as sodium and potassium move down their concentration gradient. The solute must be of appropriate size to pass through a semi-permeable membrane. By passing fluid across the membrane countercurrent to blood flow, equilibration of plasma and dialysate solute concentrations occur. This process may remove or add solute to the plasma water space depending upon the relative concentrations in dialysate and plasma. At the same time, water will also move along a gradient, in this case the osmolar or osmotic gradient, in effect "following" the solute. Diffusive clearance is more effective at removal of small solute, such as serum ions and urea, than for larger solutes.

Hemofiltration (HF) or ultrafiltration (UF) refers to convective clearance. The difference from dialysis is that pressure gradient rather than concentration gradient has its main effect on water movement. Solute movement is secondary and in conjunction with water. The transmembrane pressure difference can be adjusted as needed to remove water from the body down a pressure gradient. The flow of plasma water "drags" solute with it in the formation of ultrafiltrate. UF or HF is far superior for fluid clearance than diffusive clearance, and small solute clearance is almost identical. Slow continuous ultrafiltration (SCUF) is a term used for removing isotonic plasma water, which is indicated in patients with fluid overload such as those with CHF.

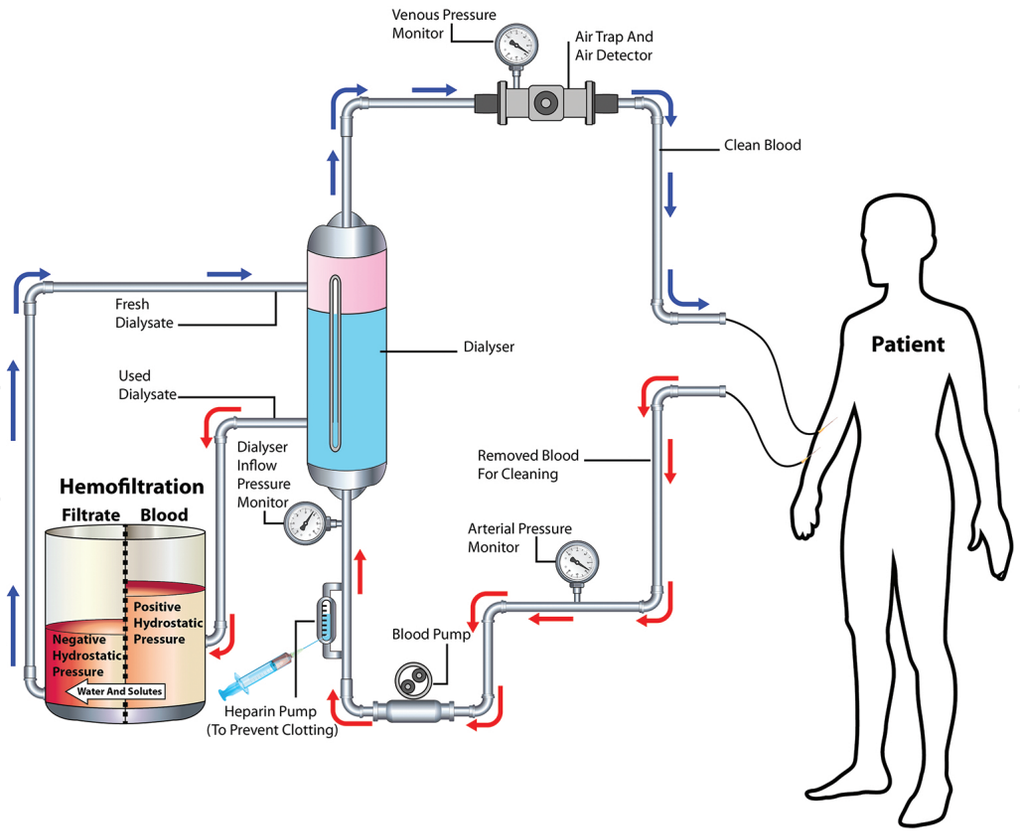

Figure 1. Principle of hemodiafiltration.

Hemodiaflitraion refers to a combination of convective and diffusive therapies. An example is the use of continuous venovenous hemodiafiltration (CVVHDF) in critically ill patients. It constitutes lower blood flow rate and slower fluid removal which may cause less hemodynamic instability in a hypotensive critically ill patient [51].

The setup for HDF requires a double-lumen central venous catheter, a peristaltic pump, and a filter inserted into a venovenous extracorporeal circuit [52] (**Figure 1**). Negative pressure generated by the pump allows blood circulation in the circuit, starting from the central vein and returning to the patient through the filter. Pore fibers of the filter keep water and small particles separated from blood through convective transport. Plasma water flow makes the blood concentration transient, eventually causing intravascular refilling while transferring liquids from the outer to the inner vascular space, thus safeguarding the circulating volume.

After the dispatched intravascular fluid is replaced by extravascular fluid refilling, hypovolemia can be prevented, thus preventing hemodynamic worsening. According to previous reported studies, fluid removal through HDF has affirmative hemodynamic effects. A study was done on 24 patients with resistant CHF undergoing UF; blood gas analysis (in both systemic and pulmonary arteries), plasma volume changes, and plasma refilling rate were measured after every liter of plasma water removed; UF was performed safely without side effects or hemodynamic instability; and mean right atrial, pulmonary artery and wedge pressures progressively reduced during the procedure [18]. Heart rate and systemic vascular resistance did not increase, and other peripheral biochemical parameters did not worsen during UF. Cardiac output increased at the end of the procedure and, to a greater extent, 24 h later, in relation to the increase of stroke volume. Intravascular volume remained stable throughout the entire duration of the procedure, indicating that a proportional volume of fluid was refilled from the congested parenchyma. Thus, UF is associated with hemodynamic improvement. Fluid refilling from the over-hydrated interstitium is the major compensatory mechanism for intravascular fluid removal, and hypotension does not occur when plasma refilling rate is adequate to prevent hypovolemia.

When a patient in decompensated heart failure is treated with HDF, it is important to ensure that the amount of removed intravascular water is below the amount of the capillary refilling rate; otherwise, neurohumoral activation can lead the patient to hypotension and abnormal renal function [18]. Thus, the distinctive feature of HDF is its effectiveness in removing extravascular fluids without increasing or decreasing the circulating volume and in turn avoiding neurohormonal activation and its consequences [52]. Respiratory symptoms such as dyspnea and orthopnea can be improved not only by total fluid removal but also by improvement in lung mechanics, pulmonary gas exchange, interstitial edema, vascular congestion, etc. [53, 54]. The two strategies (mechanical and pharmacological) of fluid withdrawal can have different effects on intravascular volume, hemodynamics, neurohumoral activity, and other regulatory mechanisms, leading to differing clinical outcomes. The tonicity of the fluid removed by the two strategies is different (isotonic with ultrafiltration [UF] and hypotonic with loop diuretics) [52, 55, 56]. With HDF, intravascular volume can be preserved, whereas it can be reduced with loop diuretics. After HDF, a better water-salt balance can be achieved and maintained in the body, whereas rapid worsening of this balance to the baseline abnormal

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state can occur with loop diuretics. A number of pathophysiology-oriented studies have documented these concepts [18, 53, 57]. Still, some ambiguity remains regarding the exact mechanisms of HDF in treating CRS and diuretic resistance.

6. Overview of clinical trials on HDF

An Israeli study aimed to determine the appropriateness and safety of UF therapy in patients with CHF who were admitted to outpatient clinics between April and September 2013 [58]. HDF was used to treat several patients with chronic CHF with NYHA III-IV and diuretic resistance. A total of 38 courses of treatment were administered. The results showed that about 1982 mL of fluid was removed per course, and patients reported having a subjective feeling of improvement in symptoms. Another Singaporean retrospective study was conducted among 44 patients who were admitted to the hospital from October 2011 to July 2013 [59] for decompensated heart failure and diuretic resistance. The study authors concluded that HDF is an effective and safe treatment strategy that can ameliorate the health of diuretic-resistant Asian patients with decompensated CHF.

Therefore, HDF has proven to be an effective method for fluid removal. It is adjustable in terms of both fluid volumes and rates with no changes in the levels of serum electrolytes. However, despite the effectiveness of HDF in fluid removal, clinical studies have not discovered any clinical benefit of this method over diuretic therapy. Furthermore, compared with diuresis, HDF does not preserve renal function.

In February 2016, a published study compared the effectiveness of HDF and loop diuresis in patients with heart failure (HF) [60]. This study comprised 105 patients with HF who were receiving UF and 108 patients with HF who were receiving adjustable loop diuretics. The aim of the study was to compare the recurrence of HF in the two groups at 90-day follow-up. However, the small sample size provided inconclusive data, which could not be used to identify a significant difference between the two patient groups. The authors of this study reported that the first HF event within 90 days of hospital discharge was seen in 25% of patients who received adjustable UF and in 35% of patients who received adjustable loop diuretics. Furthermore, there were approximately 62 days leading to the first HF event in the 25% patient group and 34 days leading to this even in the 35% patient group. Despite the trend toward better results with HDF, this difference did not reach statistical significance (log rank p 1/4 0.106). The hazard ratio, which was found to be 0.663 (95% confidence interval [CI] 0.402 to 1.092), suggested a 37% lower risk of an HF event with adjustable UF compared with adjustable loop diuretic therapy, but this result was statistically insignificant. The results should be interpreted with caution, as the study was unilateral and was prematurely terminated by the sponsor.

Another study that included 188 patients investigated UF in CRS [37]. Half of the patients were given stepped pharmacological therapy, and the other half were treated with UF. The bivariate change of the serum creatinine level and body weight from baseline, calculated after 96 h, was the primary end point of the study. The patients were then followed for 60 days. After 96 h,

patients undergoing stepped pharmacological therapy had superior renal function compared with that in patients receiving UF. A similar amount of weight loss was noted in both groups of patients. In addition, UF was found to be associated with a higher rate of adverse events.

For patients with CHF, UF is usually reserved for cases of renal failure or unresponsiveness to pharmacological therapy. To study the safety and effectiveness of UF in patients hospitalized with decompensated CHF, investigators conducted the relief for acutely fluid-overloaded patients with decompensated congestive heart failure (RAPID-CHF) trial. This study, the first randomized controlled trial to compare UF with medical therapy, comprised 40 subjects [61]. A single 8-h course of UF with peripherally inserted catheters, along with supportive care and treatment, was compared with supportive care only. Patients who received UF had a greater volume of fluid removal (median 4650 vs. 2838 mL, $p = 0.001$) and improved signs and symptoms of congestion. Treatment with UF was well tolerated by the patients and did not result in any major adverse effects such as hemodynamic and renal complications. Thus, as can be deduced from the study, early treatment with UF for patients with CHF is a feasible treatment option that is well tolerated and can result in significant weight loss and fluid removal.

Another study supporting the findings of the RAPID-CHF trial was the ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure (UNLOAD) trial [62]. The purpose of this randomized controlled trial was to study the safety and effectiveness of early treatment with primary UF in patients with ADHF. The study comprised 200 subjects with two or more signs of hypervolemia. At 48 h after the onset of treatment, weight reduction (5.0 ± 3.1 vs. 3.1 ± 3.5 kg, $p = 0.001$) and net fluid loss (4.6 vs. 3.3 L. $p = 0.001$) were higher in patients who were receiving UF. Furthermore, compared with the patients who were receiving diuretic therapy, the UF group showed lower rates of rehospitalization (0.22 ± 0.54 vs. 0.46 ± 0.76) with fewer days of in-hospital stay (1.4 ± 4.2 days vs. 3.8 ± 8.5 days) and fewer unscheduled medical visits (21% vs. 44%) within 90 days of hospital discharge. Throughout the study, changes in serum creatinine levels were similar in both groups. Episodes of hypotension during the first 48 h after hospitalization were similar (4% vs. 3%) in both groups. Thus, the UNLOAD trial demonstrated that, in patients with ADHF, UF is a safe treatment choice that produces higher weight and fluid loss compared with treatment with intravenous diuretics. In addition, UF also reduces a 90-day resource utilization in patients with ADHF. UF may thus prove to be an effective alternative to high doses of diuretic therapy in patients with ADHF, particularly in the presence of renal insufficiency.

Another small study designed for patients with ADHF investigated the effects of UF and standard intravenous diuretic (furosemide) therapy on the GFR and renal plasma flow [63]. The study comprised 19 patients who were randomized to receive UF ($n = 9$) or intravenous diuretics ($n = 10$). After treatment, no significant difference was seen in the GFR, renal plasma flow, and filtration fraction in the two groups. The difference in the net 48-h fluid removal between the two groups was also found to be insignificant. However, urine output during the first 48 h was significantly higher in the furosemide group than in the UF group.

The results of these randomized trials demonstrate that UF is associated with no major safety concerns, and compared with diuretics, it improves total fluid volume removal with decreased

hospitalizations for CHF at 90 days in selected patients. However, the clinical trials have not evaluated theoretical concerns such as predisposition to infections and bleeding complications, which can be caused by the systemic heparinization and large-bore intravenous access needed during the UF procedure.

7. Systematic reviews and meta-analyses on HDF

Recently, several meta-analyses have been performed to compare UF with diuretics for treating volume overload in patients with ADHF. The first meta-analysis comprised nine studies involving 613 patients [22]. The mean weight loss in patients receiving UF therapy was 1.78 kg (95% CI −2.65 to −0.91 kg, $p < 0.001$). This loss was more than for those treated with standard diuretic therapy. However, between the two groups, there was little difference in post-intervention creatinine levels (mean change = −0.25 mg/dL, 95% CI −0.56 to 0.06 mg/dL, $p = 0.112$). In addition, the results showed that, compared with patients treated with standard diuretics, in those treated with UF, the risk of all-cause mortality persisted (pooled risk ratio = 1.00, 95% CI 0.64–1.56, $p = 0.993$).

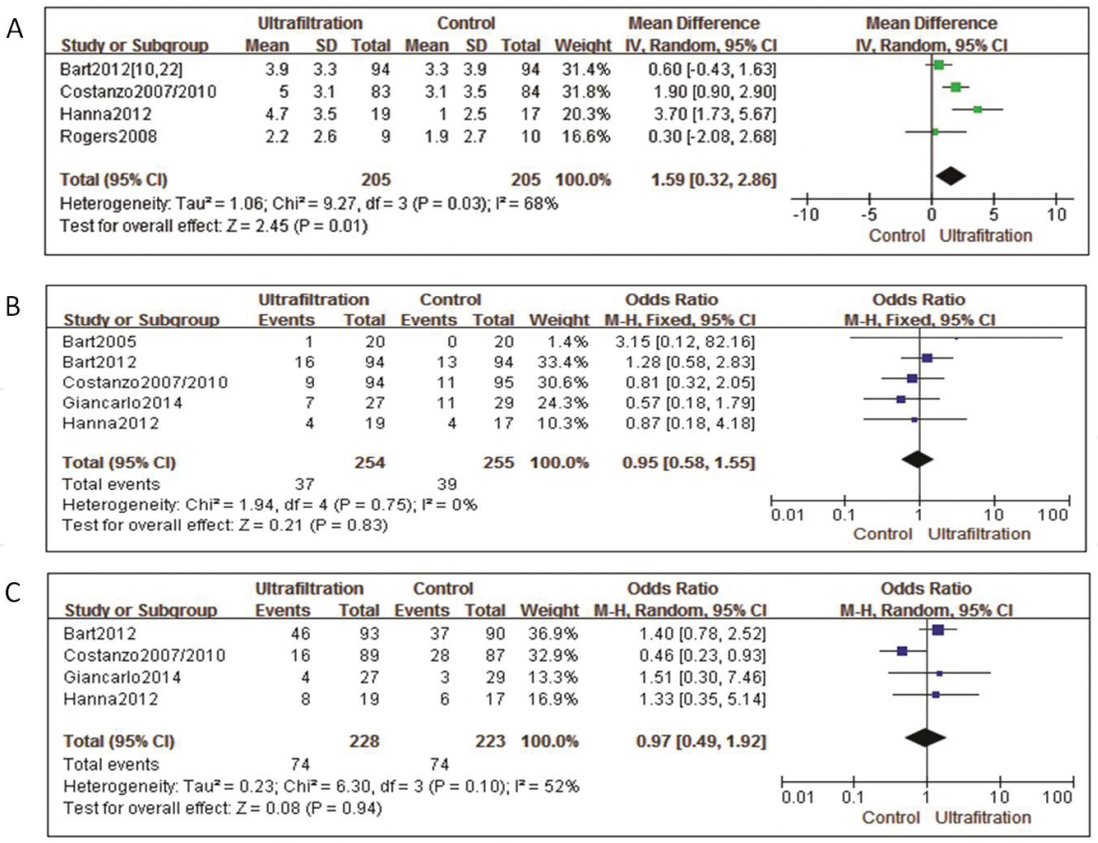

Figure 2. Forest plot of: a) Changes in weight loss at 48 h post therapy, b) all-cause mortality, c) all-cause rehospitalization. Reprinted from Cheng et al. [21], copyright with permission from International Heart Journal.

The second meta-analysis comprised seven RCTs with a total of 569 participants who met the eligibility criteria [21]. This analysis demonstrated that after 48 h of treatment, significantly higher amounts of weight loss and fluid removal were observed in the UF group compared with the diuretic group. Serum creatinine levels and changes in creatinine were found to be similar. There was no difference in all-cause mortality and all-cause rehospitalizations. In addition to these results, the authors noted that there were only minor differences between the UF and control groups in the incidence of adverse events, such as infections, anemia, hemorrhage, progressive HF, and other cardiac disorders (**Figure 2**).

8. Recommendations for the use of HDF in clinical practice

UF recommendations for HF from the 2013 guideline by the American College of Cardiology Foundation/American Heart Association Task Force [64] are shown in **Table 1**, along with recommendations from the Canadian Cardiovascular Society [65] and the European Society of Cardiology [66].

Reference	Guidelines
American College of Cardiology/ American Heart Association (2013) [64]	"Ultrafiltration may be considered for patients with obvious volume overload to alleviate congestive symptoms and fluid weight. Ultrafiltration may be considered for patients with refractory congestion not responding to medical therapy."
Canadian Cardiovascular Society (2012)[65]	"Venovenous ultrafiltration may be of benefit in relieving congestion particularly in diuretic-resistant patients"
European Society of Cardiology (2012)[66]	"Venovenous isolated ultrafiltration is sometimes used to remove fluid in patients with heart failure, although it is usually reserved for those unresponsive or resistant to diuretics."

Table 1. Recommendations and guidelines for the use of hemodiafiltration in patients with congestive heart failure.

9. HDF challenges and cost-effectiveness

Controversy still exists regarding the efficacy of HDF reported in clinical trial results to restore diuretic responsiveness in patients with CHF. The studies evaluating HDF showed considerable heterogeneity in terms of (1) study population, (2) causes of acute decompensation, (3) indications and protocols used for the prescription of HDF, (4) the "standard management" used in the control arm, and (5) end points. Marenzi et al. recommended using HDF as a complementary intervention along with diuretics rather than solely as an alternative intervention in patients with ADHF [52]. Moreover, HDF should probably be prescribed on an individual basis in diuretic-resistant patients to achieve safe decongestion. From a financial

standpoint, expenditures associated with HDF usage are still a major concern. Although initially these expenditures were considered non-prohibitive, a decision-model analysis has since found HDF to be expensive from a societal and hospital perspective. Nonetheless, for a Medicare payer, HDF can be cost-effective if existing nephrology resources such as dialysis machines, disposable supplies, and nursing staff are used as alternatives [67].

10. Conclusion

In patients with ADHF, decongestion is a major treatment goal. HDF techniques seem to be an effective tool for removal of fluid, but more robust studies are required to clarify the benefits of HDF and to characterize the group of patients who would benefit most from using it over standard diuretic therapy. Despite recent studies, crucial clinical questions are left unanswered. It is nonetheless apparent that HDF is an effective treatment strategy that should be used only for a selected group of suitable patients and performed by skilled professionals. The next research step for UF should not involve evaluating its effectiveness over that of diuretics; rather, it is more important to identify the patients who best respond to this technique to help restore their diuretic responsiveness.

Author details

Luai Alhazmi[1], Abdulelah Nuqali[2], Ankush Moza[2] and Mujeeb Sheikh[2*]

*Address all correspondence to: Mujeeb.sheikh@utoledo.edu

1 Department of Internal Medicine, University of Toledo Medical Center, Toledo, Ohio, USA

2 Division of Cardiovascular Medicine, Department of Internal Medicine, University of Toledo Medical Center, Toledo, Ohio, USA

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