Renal Replacement Therapy

REVIEW

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Is Aquapheresis ready for prime time yet for congestive heart failure? A systemic review of the literature

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Abstract

Heart failure is a clinical syndrome with considerable morbidity and mortality rates. Recent data published by National Health and Nutrition Examination Survey (NHANES) showed that 6 million Americans are diagnosed with CHF. The prevalence of CHF is expected to increase by 46% from 2012 to 2030. The current therapy for acute CHF exacerbation involves the use of oral or intravenous diuretics. Aquapheresis is a form of slow continuous ultrafiltration where blood is removed by applying negative pressure by the machine, which is then passed through the unique filter across which a set fraction of plasma water is filtered each minute before it is pumped back into the patient. It is almost exclusively used in congestive heart failure patients who are found to be resistant to incremental doses of intravenous diuretics. Several trials have shown that aquapheresis or ultrafiltration (UF) produces more significant reductions in weight and may even decrease the rehospitalization rate within 90 days; however, a greater sample size is needed to obtain results of better statistical significance. Since UF does not improve survival in patients with heart failure, limiting factors to its use include cost, the need for a multidisciplinary team, catheter-related adverse events, and renal side effects. Guidelines need to be established for its use in heart failure.

Keywords Heart failure, Aquapheresis, Ultrafiltration, Volume overload

Introduction

Heart failure is a common clinical pathology resulting from structural or functional disorders of the heart that impairs the ability of the heart to pump blood. Acute congestive heart failure (CHF) refers to the acute worsening of symptoms and signs of heart failure. Heart failure is a clinical syndrome with considerable morbidity and mortality rates. Recent data published by National Health and Nutrition Examination Survey (NHANES) showed that 6 million Americans are diagnosed with CHF. The prevalence of CHF is expected to increase by 46% from 2012 to 2030. The lifetime risk for HF could potentially increase to 45%. Heart failure (HF) is classified based on ejection fraction (EF): HF with reduced EF of < 40%, HF with preserved EF of > 50%, and HF with mildly reduced left ventricular dysfunction with EF between 40 and 50%. HF has a significant economic impact on the current healthcare system as well, with HF costs currently estimated to be $30.7 billion and approximately $69.8 billion by the year 2030. The main cost of CHF is related to the frequency of admissions and readmissions among patients with preexisting CHF [1]. The rate of survival among CHF patients has steadily increased. From 1998 to 2008, the 1-year HF mortality rate was 29.6% and has slowly declined [2]. The American College of Cardiology Foundation/American Heart Association (ACCF/AHA) has provided updated

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recommendations on managing acute heart failure. The initial therapy consists of oxygen therapy or ventilatory support, intravenous loop diuretics, intravenous vasodilators, and morphine as needed [3].

This article will focus on acute congestive heart failure and the use of diuretics and aquapheresis in its treatment.

Pathophysiology and consequences of fluid overload

The pathophysiology of congestive heart failure is a rather complex clinical syndrome in which the heart fails to pump enough blood throughout the body to meet the body's metabolic requirements. In the initial stages of CHF, the heart adapts physiological compensatory mechanisms to maintain cardiac output. Such compensatory mechanisms include myocardial hypertrophy, increased sympathetic tone, activation of the renin–angiotensin–aldosterone system, and cardiac remodeling. The increase in sympathetic tone allows for the release of catecholamines, which leads to a compensatory increase in heart rate and contractility to maintain cardiac output. In addition to increased catecholamine release, activation of the renin–angiotensin–aldosterone system (RAAS) in response to low renal perfusion leads to systemic vasoconstriction, causing an increase in arterial and venous tone. The increased arterial tone increases afterload and further decreases the ability of the heart to pump, and an increase in venous tone leads to an increase in venous return to the heart (preload). Activation of RAAS is also associated with elevated levels of ADH, which increases the circulating blood volume and contributes to an increased preload [4]. One consequence of such compensatory mechanisms is fluid overload in the form of pulmonary edema, in which an elevation of pulmonary venous pressure leads to fluid accumulation in the alveoli. This increase in alveolar pressure progresses to dysregulation of pulmonary fluid homeostasis, eventually causing dyspnea and fluid overload symptoms. Renal congestion is another consequence, causing a reduction in renal perfusion and glomerular filtration, leading to acute kidney injury development [5]. Congestive hepatomegaly is another consequence of impaired venous outflow caused by right-sided heart failure [6]. This activation of RAAS and the sympathetic system is well documented in HFrEF but only seen in a subset of patients with HFpEF [7]. The lack of significant systemic RAAS activation in HFpEF may provide a potential explanation for the limited effectiveness of RAAS inhibitors in improving outcomes in HFpEF [8]. It is marked by elevated left ventricular filling pressure caused by diastolic dysfunction, limited systolic reserve capacity during stress, arterial stiffness, and left atrial and endothelial dysfunction. Most treatment options are primarily targeted toward these compensatory mechanisms and continue to be first-line therapy for symptomatic treatment of acute CHF.

Diuretic use in acute CHF

Loop diuretics are considered first-line therapy for the symptomatic treatment of congestion in acute CHF. They are frequently used in incremental doses to increase urine output. The development of diuretic resistance limits their use. Diuretic resistance consists of failure to adequately elevate fluid and sodium (Na+) output to overcome fluid overload, edema, or congestion despite elevation in loop diuretic dosage. The mechanism of diuretic resistance consists of tubular tolerance, including enhanced reabsorption at the proximal convoluted tubule (PCT), which limits the delivery of the diuretic to the Loop of Henle, as well as increased reabsorption at the distal convoluted tubule (DCT) and collecting duct which counteracts diuretic blockade of Na+ reabsorption in the Loop of Henle [9]. In patients with diuretic resistance, aquapheresis is considered for managing symptoms and effectively reduces the number of rehospitalizations associated with acute CHF.

Aquapheresis: Concept and Use

Kidneys perform two main functions: removal of excess plasma water and uremic toxins to maintain homeostasis. These two functions can be achieved via extracorporeal devices when needed. Ultrafiltration is a process where plasma water from the vascular space is filtered across a semipermeable membrane triggered by a transmembrane pressure gradient [10].

Renal replacement therapy is a common term that refers to the combination of both ultrafiltration and clearance of uremic toxins. Multiple renal replacement therapy modalities are primarily based on diffusion and convection. Conventional hemodialysis uses both principles, diffusion for clearance of uremic toxins and convection for ultrafiltration. Hemodialysis can be either performed intermittently, every other day with each session typically lasting 3 to 4 h, or it can be performed continuously throughout the day, called continuous renal replacement therapy (CRRT). It can also be performed over 6–12 h with low blood flow and low dialysis flow, known as sustained low-efficiency dialysis (SLED). Traditional dialysis machines can also perform isolated large volume ultrafiltration over 2 to 3 h of the session.

Continuous venovenous hemodialiftration (CVVHDF) is another form of renal replacement therapy that uses convection to achieve clearance and ultrafiltration. It is typically utilized in patients with hemodynamic instability in intensive care unit (ICU) settings. Plasma water containing high levels of uremic toxins is removed by convection and replaced by a replacement fluid that does

not contain uremic toxins and has desired concentration of electrolytes. CVVH can also be performed with or without net ultrafiltration. It is postulated that acute reduction in serum osmolality during renal replacement therapy contributes to hypotension in addition to fluid removal [11]. This hypotension can lead to myocardial damage and further ischemic injury to the kidneys in acute kidney injury (AKI) [12].

When ultrafiltration is performed in isolation, the ultrafiltrate has the same concentration of urea and electrolytes as plasma water. As a result, isolated ultrafiltration does not impart a change in serum osmolarity; thus, theoretically, there is relatively less hypotension.

Ultrafiltration can be performed rapidly or slowly. Isolated slow continuous ultrafiltration is also referred to as SCUF. The terms aquapheresis, SCUF, and UF are used interchangeably. Blood is removed by applying negative pressure by the machine, which is then passed through the unique filter across which a set fraction of plasma water is filtered each minute before it is pumped back into the patient.

It is postulated that the removal of excess plasma water in heart failure patients by utilizing ultrafiltration results in the inhibition of the renin–angiotensin–aldosterone axis, which then leads to increased sodium and water excretion by the kidneys [13]. Removal of plasma water sets in motion a chain of hemodynamic changes, including a relative drop in hydrostatic pressure, which results in a refill of intravascular space by the fluid in interstitial space. If the ultrafiltration rate exceeds the plasma refill rate, transient intravascular hypovolemia can ensue, resulting in acute kidney injury.

Aquapheresis is almost exclusively used in congestive heart failure patients who are found to be resistant to incremental doses of intravenous diuretics [14].

Clinical Trials on Aquapheresis

Aquapheresis has been studied as a modality for fluid removal in patients with acute decompensated heart failure who do not respond to escalating doses of diuretics. Several clinical trials have been conducted to compare the two treatment options. Available trials have enrolled patients with HFrEF and HFpEF, and patients with mild to moderate kidney dysfunction and stable blood pressure. Patients with severe kidney impairment and hypotension were typically excluded due to potential complications.

The CARESS-HF trial [15, 16], enrolled 188 patients of the planned 200 due to a lack of evidence of benefit and several adverse events with UF. The median EF of these patients was 33%. Patients with creatinine levels up to 3 mg/dL were included. Ninety-four patients were assigned to the UF group, the other 94 were assigned to the pharmacological therapy group who received loop diuretics, and some received metolazone. At 96 h after enrollment, there was a significant increase in serum creatinine in the UF group compared to the pharmacological therapy group. There was no significant difference in weight loss between the two groups. A higher number of adverse events were noted in the UF group due to increased incidences of renal failure, catheter site and gastrointestinal hemorrhage, and intravenous catheter-related complications like sepsis and bacteremia. This study concluded that pharmacological therapy was superior to ultrafiltration. However, the safest and most effective rates of fluid removal and duration of treatment are unknown for UF, and more research needs to be done to establish specific guidelines, including when to terminate UF. In a per-protocol analysis of the CARRESS-HF trial, the authors concluded that UF was associated with greater weight loss and fluid removal compared to diuretic therapy. However, it was also associated with more adverse effects, such as hypotension and an increase in serum bicarbonate.

Older trials, including UNLOAD [17] and RAPID-CHF [18], enrolled 200 and 40 patients. Both trials included patients with HFrEF and HFpEF and required that patients have adequate urine output (> 1200 mL in the preceding 24 h). It concluded that UF results in greater weight and fluid loss than intravenous diuretics. In the UNLOAD trial, more significant weight loss was associated with decreased heart failure rehospitalization rates without a substantial difference in the rise in creatinine between the two groups. Another interesting finding from this trial was that the discharge oral diuretic doses were reduced in the ultrafiltration group and increased in the intravenous diuretic group. This observation suggests that early ultrafiltration may even improve response to diuretics. In the RAPID-CHF trial, one catheter site infection in the UF group needed four weeks of intravenous antibiotics for treatment.

The AVOID-HF trial [19], published in 2016, tested the hypothesis that patients with acute decompensated heart failure when treated with UF, will have a longer time to first heart failure event within 90 days of hospital discharge as compared to the patients treated with intravenous loop diuretics. It excluded patients with severe renal insufficiency (serum creatinine > 3.0 mg/dL). Diuretics were held in the UF group for the duration of acute decompensated heart failure treatment. Two hundred twenty-four patients were enrolled; 110 were randomized to the UF group and the rest to the diuretic group. Patients in the UF group trended toward a longer time to a first heart failure event. However, the trial was terminated prematurely by the sponsor. As a result, the sample size was much smaller than planned,

Table 1 The list of clinical trials assessing the role of ultrafiltration included in our study

Name	Year Published	Type of Study	Summary	Limitations
Ultrafiltration versus usual care for hospitalized patients with heart failure: the Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial [18]	2005	Randomized controlled trial	Early treatment with ultrafiltration in patients with acute decompensated heart failure resulted in significant weight loss and fluid removal	A small patient population was enrolled (a total of 40 patients)
Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure (UNLOAD) [17]	2007	Randomized, controlled trial	Ultrafiltration produced greater weight and fluid loss and reduced 90-day risk of rehospitalization compared to intravenous diuretics	The cost-effectiveness of ultrafiltration was not established
Ultrafiltration in Decompensated Heart Failure with Cardiorenal Syndrome (CARESS-HF) [15], [16]	2012	Randomized, controlled trial	Serum creatinine was significantly increased 96 h after enrollment in ultrafiltration group and there was no significant difference weight loss, mortality or rehospitalization compared to diuretic group	The trial was randomized but the treatment assignments were not blinded
Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) [19]	2016	Randomized controlled trial	Ultrafiltration group trended toward a longer time to the first heart failure event within 90 days of intervention	The trial was terminated prematurely by the sponsor after enrollment of 224 patients
Early continuous ultrafiltration in Chinese patients with congestive heart failure (EUC-CHF) [21]	2019	Prospective Cohort Study	A study designed to evaluate the efficacy of early ultrafiltration (within 24 h of hospital admission). The trial aims to determine if early ultrafiltration is superior to intravenous loop diuretics	A limited number of patients enrolled in two treatment groups (a total of 40)
Efficacy and safety of early ultrafiltration in patients with acute decompensated heart failure with volume overload [20]	2020	Prospective, randomized, controlled trial	Early ultrafiltration was found to be superior to diuretics (torsemide plus tolvaptan) for treatment of patients with acute decompensated heart failure	No significant differences were found in readmission and mortality rates among the two groups at 1- and 3-month follow-ups

and the differences between the two groups were not statistically significant.

In a prospective, randomized, controlled clinical trial published in 2020 by Jingyi Hu et al., 100 patients were enrolled, 40 were assigned to the early ultrafiltration group, and 60 were assigned to the torsemide plus tolvaptan group. The inclusion criteria of the study required a serum creatinine level of < 2.0 mg/dL, and enrolled patients had a mean estimated glomerular filtration rate (eGFR) of 65.3 ± 24.6 ml/min/1.73 m^2. The primary efficacy endpoint was a change in body weight and daily urine output on days 4 and 8 of treatment. Secondary efficacy endpoints included changes in brain natriuretic peptide (BNP), jugular venous pulse (JVP), and inferior vena cava (IVC) diameter. On day 4 of treatment, urine output and weight loss were significantly higher in the early UF group than in the diuretic group. On day 8, the mean urine increase was still more remarkable in the UF group. However, no differences in weight loss were measured between the two groups. There was also a more significant reduction of JVP, IVC diameter, and BNP in the UF group compared to the diuretic group reflecting better volume control with UF [20].

One prospective trial is underway in China to determine the efficacy and safety of ultrafiltration within 24 h of hospital stay, which also aims to establish a scoring system to guide UF treatment [21]. A systematic review published in January 2022 involving 14 trials, where patients with clinical signs of acute hypervolemia were treated with either UF or diuretics, concluded that UF reduces all-cause rehospitalization and it may also reduce heart failure-related rehospitalization at 30 days or less [22]. A meta-analysis published in 2016 determined that UF results in greater extraction of excess fluid, more significant weight reduction, and reduction in heart failure-related rehospitalization compared to diuretics. However, it found no survival benefits, and the renal effects of UF and diuretics were comparable [23]. On the other hand, some of the disadvantages of UF include increased cost, involvement of specialists, increased risk of bleeding due to the need for anticoagulation, higher incidence of catheter-related complications, and complications associated with central venous access [24].

A new trial, namely REVERSE-HF, started in May 2022 with an expected primary completion date of September 30, 2024, will begin enrolling patients soon. Nuwellis Inc. is conducting this multicenter, open-labeled, randomized controlled trial to compare ultrafiltration with intravenous diuretics to treat fluid overload in patients with acute heart failure exacerbation [25].

These clinical trials conducted over the years are summarized in Table 1.

Conclusion

UF is an effective method to remove excess fluid in patients with acute decompensated heart failure. It can not only be used as an alternate in patients who develop resistance to intravenous diuretics but also potentially as a first-line therapy within 24 h of admission to the hospital due to heart failure exacerbation. Several trials, as outlined above, have shown that UF produces more significant reductions in weight and may even decrease the rehospitalization rate within 90 days; however, a greater sample size is needed to obtain results of better statistical significance. Since UF does not improve survival in patients with heart failure, limiting factors to its use include cost, the need for a multidisciplinary team, catheter-related adverse events, and renal side effects. Guidelines need to be established for its use in heart failure.

Abbreviations

ACCF/AHA	American College of Cardiology Foundation/American Heart Association
CHF	Congestive heart failure
NHANES	National Health and Nutrition Examination Survey
EF	Ejection fraction
HF	Heart failure
RAAS	Renin–angiotensin–aldosterone system
PCT	Proximal convoluted tubule
DCT	Distal convoluted tubule
Na +	Sodium
CRRT	Continuous renal replacement therapy
SLED	Slow low-efficiency dialysis
CVVH	Continuous venovenous hemofiltration
ICU	Intensive care unit
AKI	Acute kidney injury
SCUF	Slow continuous ultrafiltration
BNP	Brain natriuretic peptide
JVP	Jugular venous pulse
IVC	Inferior vena cava

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Declarations

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