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Ultrafiltration for Decompensated Heart Failure: Renal Implications

Amir Kazory and Edward A. Ross

Division of Nephrology, Hypertension, and Renal Transplantation, University of Florida,
Gainesville, Florida, USA

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Corresponding Author:

Amir Kazory, MD
Division of Nephrology, Hypertension and Transplantation
University of Florida
1600 SW Archer Road
Gainesville, FL 32610-0224, USA
Tel: (352) 392-4007
Fax: (352) 392-3581
E-mail: amir.kazory@medicine.ufl.edu

Abstract

The negative prognostic impact of worsening renal function in patients with decompensated heart failure has been widely recognized. As diuretics are thought to contribute to deterioration of kidney function in this setting, attempts have been made to either spare or suppress the diuretic-related pathophysiologic mechanisms involved in this phenomenon. In this regard, extracorporeal ultrafiltration represents a novel therapy for patients with heart failure, lacking the adverse impacts of diuretics on kidney function (e.g. activation of tubuloglomerular feedback). Consequently, besides its other positive clinical outcomes, there has been much hope for ultrafiltration therapy to play a protective role against negative effects of diuretics in patients with decompensated heart failure. However, the potential biological advantage has not been confirmed by clinical studies; currently available data from recent clinical trials have so far failed to demonstrate such expected positive results possibly due to counterbalance of the potential negative effects and other not well-known mechanisms. This paper briefly reviews the relevant pathophysiological mechanisms as well as existing evidence in this area and emphasizes on the need for further studies specifically designed to explore the impact of ultrafiltration on kidney function in patients with decompensated heart failure.

Kidney in heart failure

Kidney dysfunction is common in patients with heart failure (HF) and is currently recognized as an independent risk factor for morbidity and mortality in this population (1,2,3,4). In a meta-analysis of 16 studies including more than 80,000 patients with HF, Smith et al. showed that mortality increased proportionally with worsening renal function; 7% increased risk for every 10 mL/min decrease in glomerular filtration rate (GFR) (5). Interestingly, in a study by Hillege et al. on patients with HF, it was found that renal dysfunction was even a stronger predictor of mortality than impaired cardiac function (6). While fluid overload (in the form of accumulation and re-distribution) is one of the most prominent features and consequences of HF, it has been suggested that venous congestion *per se* might be an “etiological factor” for renal dysfunction in these patients. Drazner et al. found that HF patients with increased venous pressure had significantly higher creatinine levels (7). It has also been shown that elevated levels of atrial and brain natriuretic peptides are associated with renal dysfunction in patients with HF (8). Moreover, Damman et al. found that right atrial pressure (as well as the renal blood flow or RBF) is an independent determinant of GFR in patients with HF (9). They could show that in the lower regions of RBF, there is an additive effect on GFR between increased RAP and decreased RBF (9). This novel concept expands our understanding of the pathophysiology of renal dysfunction in patients with HF and points out to a far more complex pattern than the simple phenomenon of low RBF secondary to low cardiac output.

Two distinct phenomena can complicate the management of patients with acute decompensated HF; worsening of kidney function parallel with the process of acute decompensation, and progression of renal dysfunction despite instauration of appropriate therapy. It has been shown that worsening renal function during the treatment of HF is common and that it portends poor outcomes independent of the baseline renal dysfunction (10,11,12). Although the pathophysiological mechanisms for worsening renal function in this setting remain unclear, a number of potential explanations have been offered (e.g. persistent vasoconstriction and high renal venous pressure) (13). Since worsening renal function occurs relatively early during the treatment of HF while the patients are still volume-overloaded, it has been suggested that intravascular volume depletion and pre-renal state is unlikely to be the underlying mechanism (13,14,15).

Diuretic resistance, still without a universally-accepted definition, is another kidney-related pathologic phenomenon that can further complicate the treatment of HF. While its mechanisms are beyond the scope of this article, it should be emphasized that association of diuretic resistance with worsening kidney dysfunction in patients with HF represents the extreme pathologic situation for which there are currently very few well-established therapeutic options (16,17). The practical management strategies often employed to attenuate the early stages of diuretic resistance are based on the known mechanisms of this phenomenon. Increasing the dose of the diuretic will raise its intraluminal concentration. Increased frequency of administration and use of continuous intravenous infusion would help overcome the phenomenon of post-diuretic salt retention by reducing the drug-free interval (18). The addition of thiazide diuretics (particularly the long-acting formulations) to loop diuretics portends a synergistic effect in terms of sodium excretion; it has been shown that chronic use of loop diuretics is followed by hypertrophy and hyperplasia of renal distal tubular cells with increased function of

thiazide –sensitive transporters in order to compensate for the loss of sodium from loop of Henle (19). Unfortunately, a subset of patients with HF, while responding well at the early stages of the disease, will become refractory to these management strategies over time. Some may further decompensate, and become so uremic that temporarily decreasing or discontinuing their angiotensin-converting enzyme inhibitor (ACE-I) doses may be of benefit in order to transiently restore their GFR; however, it has long been recognized that a frequently better strategy is to continue the ACE-I for its afterload effects while decreasing the diuretic dose (20).

Diuretics and tubuloglomerular feedback

Diuretics (with or without vasoactive agents) remain the mainstay of treatment for decompensated HF. The precise impact of diuretics on renal function remains controversial; while a study on healthy men with salt restricted diet reported increased GFR associated with use of furosemide, the majority of studies have found that diuretics are indeed associated with a decline in kidney function (21,22,23). It is likely that the dose of diuretics and the study population can play a role in the conflicting results reported in these studies. In HF population, Gottlieb et al. have confirmed that diuresis with furosemide can induce a decrease in GFR (23).

One plausible explanation for this phenomenon is the increased delivery of sodium to the distal tubule and macula densa resulting in constriction of the afferent artery; the so called tubuloglomerular feedback (TGF). In order to avoid deleterious effects of diuretics on renal function while treating HF, efforts have been made then to either suppress or spare macula densa and TGF activation. Activation of adenosine receptors in macula densa and afferent artery plays a major role in initiation and persistence of TGF (24), and adenosine A1 receptor antagonism seems an appealing alternative option in this setting. Indeed, it has been shown that blockade of A1 adenosine receptors is associated with enhancement of natriuresis similar to furosemide without unfavorable effects on GFR (23). Moreover, when added to furosemide therapy in patients with HF, adenosine receptor antagonists have been suggested to increase urine output while protecting against the decline in renal function (24). In order to explain the deleterious effects of diuretics on GFR, other studies have suggested that through prostaglandins, furosemide might have direct renal tubular toxicity independent of changes in renal blood flow (23,25). This hypothesis needs to be evaluated in more vigorous studies.

Neurohormonal activation plays a major role in the pathophysiology of HF and its relation to renal dysfunction. Patients with HF present with a baroreceptor-mediated increase in sympathetic tone. Increased renal adrenergic activity results in an increase in renal sodium and water absorption through a number of mechanisms including activation of renin-angiotensin-aldosterone system (RAAS) and direct effect on proximal convoluted tubules (26). These pathways in addition to an increased non-osmotic release of vasopressin form the neurohormonal pathophysiological basis for diminished renal hemodynamics in patients with HF (26).

Continuous extracorporeal therapies with pumped venovenous systems (e.g. continuous venovenous hemofiltration or CVVH) have traditionally been used for hemodynamically unstable patients with various degrees of renal dysfunction, volume overload, electrolyte abnormality, or acid-base disorders (27). These techniques may also

be used for fluid removal alone (slow continuous ultrafiltration or SCUF) for “renal support,” as in select patients with severe congestive HF and inadequate urine volume. It is noteworthy however, that the complexity of these therapies often necessitate an intensive care setting as well as presence of well-trained nurse-technicians (27). In addition, lessons learned from the use of peritoneal dialysis (PD) in end-stage renal disease (ESRD) have been useful in the design of peritoneal UF protocols for the treatment of HF (16). If PD is prescribed continuously over 24 hours (as opposed to night time cycling with dry days used in a subset of patients with ESRD), it can allow UF rates/hr that are lower than conventional intermittent HD. This is extremely helpful in management of HF patients with borderline low blood pressures (16).

Mechanical removal of sodium and water from intravascular sector via extracorporeal ultrafiltration (UF), is an appealing therapeutic option in this regard as it can theoretically spare macula densa, neurohormonal axis, and TGF activation. Although UF therapy has been used in the treatment of HF since three decades ago, it was not until very recently that a greater interest was generated with the development of newer devices and a number of more robust studies with promising results. Indeed, UF therapy could represent the principle practical method currently available for patients with diuretic resistance in whom it is highly beneficial to avoid the deleterious effects of neurohormonal activation (e.g. sympathetic nervous system and RAAS).

Ultrafiltration and the kidney; theoretical considerations

Not surprisingly, 90 percent of hospitalizations for HF are due to signs and symptoms related to volume overload and congestion (28). Since sodium retention with resultant extracellular fluid expansion is the final common pathway for the pathophysiological mechanisms involved in the development of HF (26), any therapeutic modality with greater sodium extraction than diuretics can be considered advantageous. As ultrafiltrate extracted from serum during UF therapy is isotonic, it contains significantly higher amount of sodium compared to hypotonic urine produced by diuretics (29). Therefore, UF therapy can theoretically be associated with more effective reduction in total body sodium content for equal amount of fluid removed from the body.

It has been shown that isolated elevation of central venous pressure has an adverse impact on renal hemodynamics and can directly increase sodium retention (30). UF therapy can decrease central venous pressure via direct removal of fluid from intravascular sector, leading to an increase in renal perfusion pressure, improvement in renal hemodynamics, and enhanced sodium excretion. Interestingly, Mullens et al. recently reported that in volume-overloaded patients with HF, mechanical fluid removal (via paracentesis or UF) can lead to a significant reduction in intra-abdominal pressure and improvement in renal function via venous decongestion (31).

A large number of studies have shown sustained beneficial clinical effects of UF after termination of therapy (e.g. fewer hospitalizations over the next 3 months) (32,33). Diuretic responsiveness is also reported to be restored in a number of these patients (34). While the exact mechanisms remain unclear, it has been suggested that removal of pro-inflammatory cytokines and toxins (e.g. myocardial depressant factor) might play a role in this phenomenon. Libetta et al. showed that hemodiafiltration in patients with HF is followed by significant reduction in pro-inflammatory cytokines (e.g. interleukin-8) and restoration of diuretic responsiveness over the 30 days following therapy (35). Although

similar results have been reported by other authors, it should be noted that, in contrast to UF, the extracorporeal treatment used in that study (i.e. hemodiafiltration) combines both convective and diffusive mechanisms along with high doses of replacement fluid. This will result in a much higher solute clearance compared with the traditional isolated UF therapy. Therefore, removal of pro-inflammatory cytokines, while conceivable as one of the potential mechanisms, is unlikely to be the sole explanation for sustained beneficial effects of UF. In this regard, it should be emphasized that isolated UF does not provide the clinicians with a significant solute clearance. However, once added to traditional hemodialysis, it can simultaneously correct volume overload, electrolyte abnormalities, and acid-base imbalances as well as removing uremic toxins. Moreover, in volume-overloaded HF patients with refractory acidosis, use of UF can help rapidly correct intravascular volume hence providing the opportunity to use intravenous or oral bicarbonate therapy.

The major drawback for UF from a renal standpoint would be its potential to impair renal perfusion and its sodium-sparing activity. During UF, removal of fluid from intravascular sector leads to a shift of fluid from the extravascular sector into the intravascular compartment in order to replace the loss and maintain hemodynamic stability. A mismatch between plasma refill and ultrafiltration rates thus is a major cause of intravascular volume depletion and hypotension (36). The rate of this shift (i.e. plasma refill rate or PRR) depends on a number of factors including serum albumin level, vascular permeability, and myocardial function. It is known that many patients with HF, similar to other chronic disease states and wasting syndromes, suffer from malnutrition-inflammation complex syndrome (37). Hence, it is conceivable that these patients would manifest an impaired PRR due to low serum albumin, inflammatory state, and myocardial dysfunction resulting in a very slow shift of fluid into intravascular sector during UF therapy. Since a large subset of patients with HF concomitantly present with CKD (with resultant impaired autoregulatory mechanisms), and many of them receive medications affecting renal hemodynamics (e.g. diuretics and ACE-I), the alterations in renal perfusion might lead to unfavorable consequences. Although since long ago attempts have been made to find an accurate means for precise estimation of intravascular volume during extracorporeal therapies such as hemodialysis, so far the insight and clinical judgment of experienced staff have proven to be superior to automation (38).

Besides, it is noteworthy that although the extracorporeal devices are in general highly biocompatible, there nevertheless exists a measurable degree of inflammatory reaction, with activation of various potentially deleterious cytokines (39). This might lead to renal vasodilation and reduced renal blood flow resulting in decreased GFR even in the absence of a mismatch between PRR and UF rate.

Ultrafiltration and the kidney; Clinical considerations

Despite the above-mentioned theoretical advantages, clinical studies so far have failed to demonstrate any significant improvement in renal function associated with UF (table-1) (40,41).

Table-1: Summary of studies using novel devices of ultrafiltration for heart failure

	Study Design and Protocol	Number of Patients	UF Therapy	Baseline Creatinine (mg/dl)	Post-UF Creatinine (mg/dl)	Comments
Bart et al. (45) (2005)	RCT, early single 8- hour UF plus usual care vs. usual care alone (additional courses of UF were allowed only after 24 hour goals were assessed)	40	Maximum rate was 500 ml/hr. UF group had a volume removal of 4650 ml at 24 hours.	1.6	1.9	No significant difference in renal function between UF and diuretic groups (Creatinine for diuretic group: 1.8 and 1.9 mg/dl at baseline and at 48 hours post-UF therapy respectively). UF was used as an adjunct rather than an alternative treatment.
Costanzo et al. (40) (2005)	No control group, one session of UF for each patient	20	Maximum rate was 500 ml/hr. UF stopped when symptoms resolved	2.12	2.2	No significant change in renal function.
Liang et al. (42) (2006)	No control group, number of UF sessions at the discretion of physician (1 to 5 sessions)	11	A total of 32 UF sessions each 8 hours	2.2	2.3	No significant change in mean creatinine levels. However 4 patients were dialyzed on the same admission and 1 on a subsequent admission.
Dahle et al. (41) (2006)	No control group (Case series) UF sessions stopped at discretion of physician	9	400 ml/hr for 4 hours then 200 ml/hr thereafter, Mean length of UF time: 33.3 ± 20 hours	1.4	1.4	No significant change in renal function.

Table – 1 (Cont'd)

Costanzo et al. (33) (2007)	RCT, Single session early UF therapy (within first 24 hours of admission) Duration and rate of removal at discretion of physician	200	Maximum rate was 500ml/hr. The average rate of removal 241 ml/hr for 12.3±12 hours	1.5	NR	No significant difference in renal function between UF and diuretic groups. Percentage of patients with >0.3 mg/dl rise in creatinine consistently higher in UF group at 24 hour, 48 hour, and at discharge (although statistically not significant).
Jaski et al. (46) (2008)	No control group, retrospective cohort, each patient with one or more sessions of UF therapy	100	2 to 6 liters of fluid removed over 8-12 hours in each session. (total: 7 L during 2.1 sessions per hospitalization)	1.8	1.9	No significant change in renal function.
Rogers et al. (44) (2008)	RCT, single session UF therapy; Exclusive UF therapy during the first 24 hours of admission (substudy of UNLOAD trial)	20	Maximum rate was 500ml/hr.	GFR of 37 ml/min	NR	No significant difference in GFR, RBF, and FF between UF and diuretics groups. Iothalamate was used to measure GFR; it decreased by 3.4 and 3.6 ml/min in UF and diuretic groups respectively.

UF: ultrafiltration, RCT: randomized controlled trial, GFR: glomerular filtration rate,

RBF: renal blood flow, FF: filtration fraction, NR: not reported

Liang et al. used UF for 11 patients with refractory HF and diuretic resistance (42). Surprisingly, not only they did not observe any significant change in the average creatinine levels, but also 45% of the patients experienced worsening renal function as defined by an increase in serum creatinine of greater than 0.3 mg/dl. Moreover, 5 of the 11 patients required dialysis on the same or subsequent admission. The largest randomized controlled trial that compared UF therapy with high dose intravenous diuretics in patients with decompensated HF, again failed to show any significant difference in terms of change in serum creatinine levels between the two groups (33). Indeed, the UF group had even a trend towards higher serum creatinine levels at the majority of time points.

It is noteworthy that a number of HF patients might experience improvement in renal function with volume removal. Therefore, reporting the mean creatinine levels or even the mean changes in serum creatinine concentration may not accurately reflect a significant subset of patients with worsening renal function (i.e. those with poorer outcomes). Besides, it has been suggested that serum creatinine levels as well as creatinine-based formulas should be cautiously interpreted for evaluation of GFR in HF population (43). Therefore, it can be argued that previous studies did not use the accurate means for measurement of true renal function while comparing the impact of UF and diuretics in patients with HF. Nevertheless, a recent study by Rogers et al. specifically addressed this question using iothalamate and para-aminohippurate to meticulously measure GFR and renal plasma flow (RPF) respectively. Surprising to many investigators, no difference in GFR, RPF, or filtration fraction could be found between UF and furosemide groups (44). Although this trial suffers from a number of limitations (e.g. small study population), it is the first study with a head-to-head controlled comparison of the impact of UF and diuretics in a very precise manner. The fact that the results of this randomized controlled trial are actually in agreement with the results of the previous larger but less specific studies, make the conclusions of the authors more reliable.

It should be emphasized that the impact of UF on renal function has not been the primary endpoint in the majority of these studies. However, once evaluated only as a secondary safety endpoint, UF has not been reported to portend any statistically-significant deleterious or beneficial effect on renal function. As mentioned earlier, the only study that evaluated the impact on renal function as the primary endpoint found that the use of UF was associated with a decline in renal function similar to diuretics (44).

In summary, from a theoretical point of view, UF has a number of potential kidney-related advantages compared to diuretics and has even been suggested to portend protective effects against the adverse impacts of diuretics on kidneys. However, currently available clinical studies do not confirm this concept possibly due to counterbalance of potential negative impact of UF on kidney function. Future larger studies specifically designed to measure renal clearance capacity are clearly needed to further verify the impact of UF on kidney function in HF population.

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