Should Ultrafiltration Be Used Preferentially Instead of Diuretics for the Initial Treatment of ADHF Patients?

**Treatment of Congestion in Congestive Heart Failure**

Ultrafiltration Is the Only Rational Initial Treatment of Volume Overload in Decompensated Heart Failure

*Bradley A. Bart, MD*

“"If you have always done it that way, it is probably wrong.”
—Charles F. Kettering, 1876–1958

The morbidity of decompensated heart failure is due to volume overload, a consequence of increased total body sodium. Failure to adequately reduce total body sodium contributes to progressive ventricular dysfunction, worsening heart failure, and excess morbidity. Ultrafiltration is the gold standard for sodium-volume removal and is the only intervention shown to improve outcomes in a randomized controlled trial of patients hospitalized with decompensated heart failure. Diuretics are inherently inferior because they produce hypotonic urine and undesirable hemodynamic and neurohormonal changes. Therefore, ultrafiltration is the preferred initial treatment for patients hospitalized with decompensated heart failure and sodium-volume overload.

Response by Shin and Dec on p 504

Sodium is the Major Determinant of Extracellular Fluid Volume

The earliest descriptions of heart failure date back more than 3500 years to the Egyptian civilization. Even then, symptoms were correctly attributed to volume excess. It was not until the early 20th century that researchers recognized the role of salt in the formation of edema. In 1901, researchers found that salt fed to patients with congestive heart failure could not be recovered as chloride in the urine. This represents one of the earliest descriptions of heart failure as a sodium avid state. Later, it was demonstrated that liberal salt intake increased congestive symptoms and pulmonary edema in patients with heart failure whereas patients on salt-restricted diets could tolerate large amounts of water without any further increases in congestion or edema. Other studies confirmed the primary role of salt, not water, in the formation of edema in heart failure. By 1948, sodium was widely recognized as the major determinant in extracellular fluid volume.

Today, it is understood that sodium retention in heart failure is under the influence of the sympathetic and renin-angiotensin-aldosterone (RAAS) systems. Renin release from the kidneys leads to the production of angiotensin II. Increased angiotensin II levels activate receptors on the epithelium of the proximal tubule enhancing sodium reabsorption in the nephron. Angiotensin II also causes constriction of the efferent arterioles disturbing the usual balance of hydrostatic and osmotic forces in the peritubular capillaries such that sodium reabsorption is increased. In addition to its direct tubular and vascular effects in the kidney, angiotensin II promotes aldosterone secretion. Aldosterone increases sodium reabsorption in the distal nephron. Decreased sodium
and water delivery to the distal nephron stimulates the macula densa to increase renin synthesis. Thus, sodium retention is part of a feedback loop that amplifies the sympathetic and RAAS systems.

**Consequences of Sodium-Volume Overload**

Sodium retention has a profound effect on vascular function and the pathogenesis of hypertension. Excess sodium inhibits the Na+/H+ and K+/H+ ATPase of arterial and arteriolar vascular smooth muscle cells stimulating the sodium-calcium exchanger. This leads to increased intracellular calcium levels and vasoconstriction. In addition, sodium retention decreases the synthesis of nitric oxide and increases levels of asymmetrical dimethylarginine, an endogenous inhibitor of nitric oxide production.

Sodium retention also causes obligatory (passive) water accumulation that ultimately leads to increased extracellular fluid volume and increased left and right-sided pressures. Elevated left-sided pressures result in pulmonary congestion, which is recognized clinically by dyspnea on exertion, orthopnea, cough, hemoptyisis, rales, and characteristic radiographic findings. High left-sided pressures also cause left ventricular chamber dilation and distortion of the mitral annulus often leading to malcoaptation of the mitral valve leaflets and significant mitral regurgitation. Left ventricular chamber dilation increases wall tension and myocardial oxygen demand to the extent that myocardial ischemia and/or necrosis may occur. Functional mitral regurgitation and myocardial ischemia or necrosis adversely affect cardiac output ultimately leading to worsening symptoms, further activation of the sympathetic and RAAS systems, increased sodium retention and acceleration of cardiac remodeling (Figure 1).

Elevated right-sided pressures can lead to cardiac interstitial edema, myocardial contractile dysfunction, and interventricular dependence, factors that adversely affect stroke volume and cardiac output. Elevated venous pressures also cause clinically important reductions in renal blood flow, glomerular filtration rate, and sodium excretion. Thus, congestion of the kidney perpetuates the cycle of sodium retention, venous congestion, reduced kidney function, and sympathetic and RAAS activation.

**Treatment of Congestion: It’s the Salt**

Most patients with heart failure suffer from symptoms of congestion. When these symptoms become severe, patients are hospitalized and treated with diuretics — an approach that has remained essentially unchanged since the 1960s. Unfortunately, the outcomes of patients hospitalized with decompensated heart failure remain poor in spite of (or due to) the nearly universal use of diuretics: 2% to 22% of patients die during the acute hospitalization, 44% are readmitted within 6 months, and 33% are dead within 1 year. Given these sobering statistics, we must carefully reexamine the use of diuretics in treating decompensated heart failure if we wish to improve on these dismal outcomes.

**Loop Diuretics Are Inefficient and Difficult to Use**

Loop diuretics such as furosemide act on the luminal surface of the ascending loop of Henle to block the sodium-potassium-chloride transporter. This results in an increase in urinary excretion of sodium, chloride, calcium, magnesium, and potassium. Although urinary excretion of sodium is increased, urine remains hypotonic relative to extracellular fluid because only 25% of the filtered sodium load is normally reabsorbed by the thick ascending limb; the proximal and distal convoluted tubules are responsible for the rest of sodium reabsorption in the nephron thereby limiting the amount of sodium excretion that can be achieved with loop diuretics.

The production of hypotonic urine limits the effectiveness of loop diuretics in reducing total body sodium. For example, excess fluid volume in patients with heart failure contains isotonic fluid \( \approx 140 \text{ mEq/L} \) of sodium. A recent study of
patients hospitalized for decompensated heart failure showed that the average urine concentration of sodium after the administration of furosemide was 60 mEq/L. Therefore, for every liter of urine produced in response to loop diuretics, 80 mEq of excess sodium remains unresolved. If a patient is congested with 10 L of excess fluid volume, treatment with loop diuretics would lead to 800 mEq of unresolved sodium excess (18.4 g). Persistent sodium excess results in reaccumulation of water leading to congestive symptoms, progressive ventricular dysfunction, worsening heart failure, and excess morbidity. There are a number of other well-established limitations to loop diuretics (Table). Diuretic resistance is common and contributes to high inter- and intra-individual dose responses. Diuretics are associated with potentially life-threatening electrolyte abnormalities, photosensitivity, skin rashes, interstitial nephritis, gout, hearing loss, and bone loss. Acutely, loop diuretics adversely affect hemodynamics and stimulate the sympathetic and RAAS systems. These hemodynamic and neurohormonal changes limit the effectiveness of subsequent doses of loop diuretics by reducing glomerular filtration rate.

The Evidence Base for the Use of Loop Diuretics Is Weak

The safety and efficacy of loop diuretics in patients hospitalized for heart failure has not been established by randomized controlled trials. Such studies are difficult to perform because diuretics are deemed to be necessary in patients with decompensated heart failure. In one study, patients with acute pulmonary edema and hypoxemia were randomized to escalating doses of intravenous (IV) nitrates or furosemide after receiving oxygen, morphine, and a single 40 mg dose of furosemide. Acute treatment in both groups continued until oxygen saturation increased to at least 96% or mean arterial pressure decreased by at least 30% or <90 mm Hg. During the first hour of therapy, patients in the nitrates group received a mean dose of isosorbide dinitrate of 11.4 mg and a mean dose of furosemide of 56 mg. Patients in the furosemide group received a mean dose of isosorbide dinitrate of 1.4 mg and a mean furosemide dose of 200 mg. Compared with patients in the nitrates group, patients treated with increasing doses of furosemide experienced more myocardial infarctions (36% versus 17%, P=0.047), required more mechanical ventilatory support (40% versus 13% P=0.0041) and experienced less improvement in oxygen saturation (+13% versus +18%, P=0.0063). Retrospective analyses of patient registries and clinical trials show a consistent dose-dependant association between loop diuretics and increased mortality and rehospitalization. This evidence base should raise concern about the ongoing use of loop diuretics in decompensated heart failure.

Treating Decompensated Heart Failure Without Substantially Reducing Total Body Sodium Does Not Work

EVEREST tested the hypothesis that removal of hypotonic fluid improves outcomes in patients hospitalized for congestion and decompensated heart failure. More than 4000 patients were randomized to receive standard care plus placebo or standard care plus the arginine vasopressin antagonist tolvaptan. Tolvaptan improved dyspnea, edema, and body weight in the short term but did not reduce all-cause mortality, cardiovascular death, or rehospitalization for heart failure (the dual primary end points of the trial). These results are not surprising in light of sodium’s role as the major determinant of extracellular fluid volume—failure to adequately address total body sodium excess does not improve outcomes in this patient population.

Ultrafiltration Is the Preferred Initial Treatment of Volume Overload in Decompensated Heart Failure

Ultrafiltration is the standard by which all other treatments for sodium-volume overload should be measured. Ultrafiltration is the mechanical removal of fluid from the vasculature. Hydrostatic pressure is applied to blood across a semipermeable membrane to separate isotonic plasma water from blood. Because solutes in blood freely cross the semipermeable membrane, large amounts of fluid can be removed at the discretion of the treating physician without affecting any change in the serum concentration of electrolytes and other solutes.

Ultrafiltration has been used to relieve congestion in patients with heart failure since the 1970s. In contrast to the adverse physiological consequences of loop diuretics, numerous studies have demonstrated favorable responses to ultrafiltration. Such studies have shown that removal of
large amounts of isotonic fluid relieves symptoms of congestion, improves exercise capacity, improves cardiac filling pressures, restores diuretic responsiveness in patients with diuretic resistance, and has a favorable effect on pulmonary function, ventilatory efficiency, and neurohormone levels.33–46

The evidence base supporting the use of ultrafiltration is superior to that for loop diuretics. There are 5 randomized controlled trials of ultrafiltration in patients with heart failure. In 2 small trials, patients with mild heart failure were randomized to ultrafiltration or continued medical care. Compared with ongoing medical therapy, patients treated with ultrafiltration experienced improved hemodynamics, diastolic filling parameters, neurohormonal responsiveness, and exercise capacity.34,36 A similar trial was subsequently performed with an active control arm by the same investigative team. Sixteen patients with mild heart failure were randomized to ultrafiltration (500 mL/hr) versus IV furosemide (IV bolus followed by continuous infusion-average dose 248 mg). All patients were treated until there was a 50% decrease in right atrial pressure. Exercise capacity measured by peak oxygen consumption improved significantly in patients treated with ultrafiltration and did not change in patients treated with furosemide. Body weight, right atrial, and pulmonary capillary wedge pressures fell significantly in both groups. However, these variables rapidly returned to baseline in the furosemide-treated group and were sustained in patients treated with ultrafiltration (Figure 2).33

There are 2 randomized controlled trials of ultrafiltration in hospitalized patients with congestion and decompensated heart failure. RAPID was a feasibility study comparing a single 8-hour course of peripheral venovenous ultrafiltration within the first 24 hours of admission to usual care with IV diuretics in 40 patients. This study was small, but demonstrated that ultrafiltration in this setting was safe and effective compared with IV diuretics.47 In UNLOAD, a larger follow-up study, 200 patients hospitalized with decompensated heart failure and congestion were randomized to undergo early ultrafiltration versus standard care with IV diuretics. Patients in the ultrafiltration group received no diuretics for the first 48 hours of hospitalization and their volume status was managed exclusively by ultrafiltration. Patients in the standard care group were treated with IV diuretics at doses not <2 times their usual outpatient diuretic dose given IV. Patients undergoing ultrafiltration had significantly greater weight loss at 48 hours compared with standard care. In addition, rehospitalizations for heart failure at 90 days (a prespecified secondary end point of the study) were significantly reduced in the ultrafiltration group compared with standard care (Figure 3).3 Even after adjusting for differences in weight loss between the ultrafiltration and standard care groups, ultrafiltration was independently associated with improved outcomes.48

These randomized controlled trials demonstrate that the clinical benefit of ultrafiltration is not solely related to the volume of fluid removed. Greater sodium removal during ultrafiltration (isotonic plasma water) compared with furosemide (hypotonic urine) explains sustained improvements in weight, exercise capacity, filling pressures, and rehospitalization rates.

Figure 2. Ultrafiltration results in sustained decreases in body weight and improved functional capacity compared with IV furosemide. These results are from a randomized controlled trial of ultrafiltration versus IV furosemide in heart failure patients. Treatments were continued in both treatment groups until right atrial pressure was reduced by 50%. Adapted with permission from Agostoni et al.33

Figure 3. Ultrafiltration reduces 90-day rehospitalizations for heart failure compared with standard care with IV diuretics. These results are from a randomized controlled trial of early venovenous ultrafiltration versus standard care with IV diuretics in patients hospitalized with decompensated heart failure. Adapted with permission from Costanzo et al.3

Summary
The morbidity of decompensated heart failure is due to volume overload, a consequence of increased total body sodium. Treatments that do not adequately reduce total body sodium are ineffective. As a result, using diuretics to produce hypotonic urine or other agents to achieve hemodynamic targets will not lead to improved clinical outcomes. Ultrafiltration is the gold standard for sodium-
volume removal and is the only intervention shown to improve outcomes in a randomized controlled trial of patients hospitalized with decompensated heart failure. The success of any new intervention designed to improve outcomes in this patient population should be measured against ultrafiltration.

Disclosures

None.

References

Response to Bart

Jordan T. Shin, MD, PhD; G. William Dec, MD

“Le mieux est l’ennemi du bien”
—Voltaire

Is ultrafiltration really the only rational treatment of volume overload in acute decompensated heart failure? Current American College of Cardiology/American Heart Association guidelines recommend diuretics first (class I) and ultrafiltration second (class IIA for refractory, volume overload) and do not support the statement that ultrafiltration is “the gold standard for sodium/volume removal.” Although solid data supports an adverse impact of sodium retention, it remains unclear whether enhanced sodium removal improves outcomes, as is highlighted by questions raised by the use of natriuretic peptides. Whereas some studies suggest that diuresis promotes an adverse neurohormonal milieu, others have demonstrated that acute lowering of ventricular filling pressures is associated with a decline in these measures as well as B-type natriuretic peptide. All positive survival trials in heart failure were done with the background of diuretic therapy. Thus, the argument that diuretics in and of themselves are detrimental should be tested rigorously before being accepted. As we highlight, the association between higher diuretic dose and increased mortality was based on retrospective post hoc analyses that lacked adjustment for severity of illness; these findings have not been borne out (cf. our reference 15). The argument that ultrafiltration provides superior fluid removal, weight loss, and length of stay is inconsistently supported in current trials, and additional trials are needed before these findings should be accepted generally. Although diuretics are an imperfect tool for the treatment of acute decompensated heart failure, they are a “good” therapy and should remain the gold standard until additional evidence proves the “better” approach.
Should Ultrafiltration Be Used Perferentially Instead of Diuretics for the Initial Treatment of ADHF Patients?

Ultrafiltration Should Not Replace Diuretics for the Initial Treatment of Acute Decompensated Heart Failure

Jordan T. Shin, MD, PhD; G. William Dec, MD

Heart failure (HF) represents a significant and growing health concern in the aging population of the United States. Total HF costs in the United States for 2009 are estimated to be $37.2 billion and account for more than 1 million hospital discharges.1 Acute decompensated HF (ADHF) represents the most common reason for HF hospitalization. Improvements in HF care would thus have a broad impact on health care delivery.

Response by Bart on p 511

Registry data indicate that the population of patients admitted for HF represents an “at risk” group. Acute in-hospital mortality ranges from 3% to 7% for ADHF and may be as high as 13.5% at 3 months after discharge. Furthermore, surviving patients remain at significant risk for hospital readmission (24% to 31%) within 3 months after their index hospitalization for ADHF.2 Strategies to understand the mechanisms of disease associated with poor outcomes in HF have identified a clinical syndrome of deteriorating renal function, diuretic unresponsiveness, and impaired natriuresis, which has been called the cardiorenal syndrome (CRS). Chronic renal insufficiency, commonly associated with HF, adversely impacts HF survival, length of stay (LOS), and readmission rates.3,4 Although no broadly accepted consensus definition of CRS has been adopted,5 most criteria for CRS include (a) HF and renal insufficiency; (b) worsening renal function during treatment for ADHF; and (c) diuretic resistance.6 Worsening renal function (defined by an increased serum creatinine [sCr] ≥0.3 mg/dL) is a common feature in patients admitted for volume overload and treatment of ADHF, with some reports identifying a prevalence of >70% in hospitalized patients. Treatments to mitigate diuretic resistance and CRS have been sought to promote better ADHF outcomes.

An emerging literature suggests an important role for venous congestion as a major contributor to CRS. Traditionally cited mechanisms for worsening renal function include (a) systemic and renal hypoperfusion, (b) periodic intravascular or arterial volume depletion, (c) excessive stimulation of vasoconstrictor neurohormones such as angiotensin, and (d) increased interstitial fibrosis associated with the chronic use of furosemide.7 However, recent data implicate elevated right-sided venous pressures and increased intraperitoneal pressure due to ascites, which commonly accompany right HF in the worsening renal function seen in ADHF.8–10 Thus, acute therapies directed at relieving venous congestion should be paramount in ADHF.

The pharmacological armamentarium for treating symptomatic volume overload has changed very little during the past 3 decades and remains memorialized in the mnemonic LMNOP (L indicates lasix or loop diuretic; M, morphine; N, nitrates; O, oxygen; and P, positive pressure ventilation).
frequently learned during medical training to remember acute treatments for HF. Intravenous (IV) administration of loop diuretics (identified in the “L” of the mnemonic) is effective in decreasing elevated venous filling pressures and remains the consensus first-line treatment of volume overload and congestion.11 Nearly 90% of patients in the Acute Decompensated Heart Failure National registry received IV diuretics for acute congestion during their admission.12

Improvement in ventricular filling pressures with diuretics has been shown to be strongly associated with improved survival after hospital discharge.13 Loop diuretics are efficacious for the symptomatic relief of volume overload as well as reducing intracardiac and intravascular filling pressures in HF. The usual maneuver to overcome diuretic resistance is to administer increasing doses of diuretics. However, higher doses of furosemide have been linked to higher all-cause mortality rates in retrospective observational studies.14 More recent data suggest that this association may be incorrect. In a recent prospective analysis of 183 patients with advanced HF stratified patients by baseline diuretic dose (furosemide <80 mg or >80 mg daily), patients receiving high-dose diuretics (n=113) had more markers of increased cardiovascular risk and were more likely to have had a recent history of clinical instability (33% versus 4%). After adjusting for clinical stability, diuretic dose was no longer a significant predictor of increased risk.15 Whether this association is a direct effect of the loop diuretic or simply represents a marker for more advanced HF remains uncertain.

Ultrafiltration (UF) for acute short-term fluid removal and decongestion in ADHF has been cited in the medical literature for >3 decades and represents an alternative to increasing doses of diuretics for decongestion in CRS. However, the Food and Drug Administration approval of the Aquadex system (CHF Solutions, Brooklyn Park, Minn) introduced the possibility that UF could be applied routinely in the clinical treatment of ADHF. This system can be used outside the intensive care unit setting, with only peripheral IV access. Advantages of this novel system include16 (a) reliable, consistent isotonic fluid removal; (b) implementation of a relatively simple prescription or target in patients with known “dry” weight; (c) indifference to HF mechanism (ie, systolic versus diastolic); (d) a small amount of extracorporeal blood; and (e) implementation using peripheral IV access (and other mechanisms reviewed in Table 1). Several recent clinical studies suggesting possible beneficial effects have stimulated real interest in the HF community for applying this new technology to ADHF management. As the Aquadex system is currently the only approved unit for HF, our discussion focuses on trials using this system. Principal findings of the major published studies using the Aquadex system are summarized in Table 2.

Jaski et al17 published the first report of UF accomplished through peripheral IV access with the precursor to the Aquadex system in 2003. (This study has been retrospectively referred to as the SAFE study.) This clinical series was designed to demonstrate the feasibility of fluid removal with peripheral UF in both inpatients and outpatients. Ultrafiltration was terminated after 1 L of fluid had been removed or after a total duration of 8 hours of treatment. The primary end point of 1 L of fluid removal was achieved in 23 of 25 treatments (92%). No major adverse events were recorded. Methodological shortcomings included the nonrandomized study design, small sample size, and the lack of data collection and reporting on renal function or clinical outcomes.

The RAPID-CHF trial prospectively tested whether peripheral UF was safe and effective for fluid removal and decongestion in ADHF.18 This multicenter, controlled trial enrolled patients with HF who were randomized to receive either UF or usual HF care including diuretics. UF patients received a single 8-hour treatment followed by an initial study assessment at 24 hours. Subsequent UF treatments were permitted after the initial assessment. The primary end point was weight loss at 24 hours after enrollment; secondary end points included fluid removal at 24 and 48 hours after enrollment and symptom scores, serum electrolytes, and length of hospital stay. Despite a significant difference in fluid removed both at 24 and 48 hours, there was surprisingly no difference between the primary end point of weight loss between the standard care and UF treatment groups. Subjective dyspnea

### Table 1. Potential Advantages and Disadvantages of UF Therapy

<table>
<thead>
<tr>
<th>Potential advantages of UF therapy</th>
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<tr>
<td>- More rapid removal of fluid excess and improvement in symptoms</td>
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<td>- Higher clearance of sodium load</td>
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<tr>
<td>- Isotonic fluid removal</td>
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<tr>
<td>- Decreased risk of electrolyte abnormalities (ie, hypokalemia)</td>
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<td>- Decreased risk of worsening renal function</td>
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<td>- Lack of activation of the renin-angiotensin-aldosterone system</td>
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<td>- Lack of activation of the sympathetic nervous system</td>
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<td>- Removal of proinflammatory cytokines (with potential restoration of</td>
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<td>diuretic responsiveness)</td>
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<td>- Shortened LOS for heart failure hospitalizations</td>
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<td>- Decreased rate of readmissions for heart failure</td>
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<table>
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<tr>
<th>Potential complications and disadvantages</th>
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<td>- Significant cost per procedure (device plus disposables)</td>
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<td>- Additional nursing training and staffing required</td>
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<tr>
<td>- Excessive volume removal resulting in hypotension, worsening prerenal</td>
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<td>azotemia, or acute renal failure</td>
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<tr>
<td>- Allergic reaction to the extracorporeal circuit</td>
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<tr>
<td>- Catheter-related complications (infection and thrombosis)</td>
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<tr>
<td>- Hemorrhage-complicating systemic anticoagulation</td>
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<tr>
<td>- Hemorrhage from venous return disconnection</td>
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<tr>
<td>- Air embolism</td>
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<tr>
<td>- Hemolysis and hyperkalemia</td>
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<tr>
<td>- Higher clearance of sodium load</td>
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Adapted from Kazory and Ross.16
and CHF scores improved in both treatment groups, although UF-treated patients had a greater improvement in both scores compared with diuretic-treated patients. In addition, no difference was observed in hospital LOS (6 days versus 5 days in UF and standard of care patients, respectively). Although this trial did show benefits in volume removed and subjective symptom scores, it failed to meet statistical significance for its primary end point and did not show any difference in hospital LOS.

Costanzo et al19 published their experience with early and aggressive UF in 20 patients with HF in the EUPHORIA study. Inclusion criteria for this uncontrolled observational study included volume overload, a modest degree of chronic renal dysfunction (sCr ≥1.5 mg/dL) and a relatively high-diuretic requirement at baseline. Key features of this study included (a) the short (<12 hour) hospitalization allowed before enrollment, which resulted in a mean time to initiation of UF of 4.7 ± 3.5 hour; and (b) the use of continuous UF until ADHF symptoms had resolved, unlike previous studies that allowed only an initial 8-hour UF run. In this case series, an average of 8654 ± 4205 mL were removed during UF treatment. The mean baseline sCr was 2.12 ± 0.60 mg/dL and did not change with UF treatment at discharge or at 90-day follow-up. The mean weight decreased and remained decreased at the 90-day follow-up point. The average duration of hospitalization in this series was 3.7 ± 1.8 days with 60% of patients discharged ≤3 days, likely reflecting the aggressive approach to screening and initiating UF. In the 30 days before UF treatment, there were 10 admissions for ADHF in 9 study patients; conversely, only 1 readmission was observed in the study population in the 30 days after UF treatment. On the basis of a comparison with historical control from Acute Decompensated Heart Failure National Registry, the authors conclude that UF decreases LOS and readmissions. However, the authors’ conclusion that readmission rates were decreased after UF by comparing the treatment group with the pretreatment period, rather than with a randomized control cohort, lacks statistical rigor.

Liang et al20 presented their experience with 11 serial patients treated with UF at the Mayo Clinic. Patients in this report were generally sicker and had been treated in hospital longer than the other UF studies; they had failed at least 1 IV treatment and were hospitalized an average of 4.4 ± 4.0 days before initiation of UF. These authors implemented intermittent UF treatment with the goal of removing 4 L per 8 hour of UF (a fluid removal rate of 500 mL/h, the maximum of the Aquadex UF system). The 11 patients received a total of 32 UF treatments. The mean baseline sCr was 2.2 ± 0.25 mg/dL and rose to 2.5 ± 0.37 mg/dL after treatment. Strikingly, 45% of this patient population experienced an increase in sCr > 0.3 mg/dL, and 5 of 11 patients received dialysis at the same or during a subsequent hospitalization. The 6-month mortality rate was 55%, underscoring the baseline severity of illness in the study population. Adverse events associated with the treatment were common and ranged from low-flow rates and positional variation in flow (8 of 11 patients) to bleeding complications because of systemic anticoagulation.

The UNLOAD trial, a randomized multicenter controlled trial of 200 patients with ADHF that compared UF with standard IV diuretic treatment, represents the single best-designed clinical trial that evaluated UF for the treatment of ADHF.21 The primary end points were weight loss and dyspnea score at 48 after enrollment. Secondary end points included net fluid loss and rehospitalization rates. At 48 hour, the UF group had lost significantly more weight and fluid than the diuretic cohort. Dyspnea scores did not differ between groups. The HF readmission rate was statistically lower in the UF group (32% versus 18%) as was the number of unscheduled follow-up visits (44% versus 21%). Neither sCr (baseline 1.5 mg/dL) at hospital discharge nor LOS differed between treatment groups. Furthermore, the trial design mandated that the IV diuretic dose be at least double that of the daily outpatient dose during the first 24 hours. Based on the results reported, the mean diuretic dose was 180 mg/daily, whereas baseline diuretic dose averaged 120 mg daily; these findings suggest a less aggressive approach to fluid removal in this cohort. Finally, information is lacking concerning total rehospitalization rates between the 2 groups.

The latest American Heart Association/American College of Cardiology practice guidelines fail to recommend UF as a class I therapeutic option for ADHF (see below). This reflects not only the newness of the device but also the absence of

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**Table 2. Principal Findings of UF Trials Using the Aquadex System**

<table>
<thead>
<tr>
<th>Name</th>
<th>Reference</th>
<th>Year</th>
<th>Trial Design</th>
<th>Patients</th>
<th>Symptoms</th>
<th>Weight Loss</th>
<th>Fluid Removal</th>
<th>LOS</th>
<th>Readmission</th>
<th>SCr</th>
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<tr>
<td>SAFE</td>
<td>Jaski et al17</td>
<td>2003</td>
<td>CS</td>
<td>21</td>
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<td>E</td>
<td>NA</td>
<td>NA</td>
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<td>RAPID-CHF</td>
<td>Bart et al18</td>
<td>2005</td>
<td>RCT</td>
<td>40</td>
<td>↓ *</td>
<td>NS</td>
<td>↓ *</td>
<td>NS</td>
<td>NA</td>
<td>NS</td>
</tr>
<tr>
<td>EUPHORIA</td>
<td>Costanzo et al19</td>
<td>2005</td>
<td>CS</td>
<td>20</td>
<td>E</td>
<td>E</td>
<td>E</td>
<td>↓ *</td>
<td>↓ *</td>
<td>NS</td>
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<td>—</td>
<td>Liang et al20</td>
<td>2006</td>
<td>CS</td>
<td>11</td>
<td>E</td>
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<td>E</td>
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<tr>
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<td>2007</td>
<td>RCT</td>
<td>200</td>
<td>NS</td>
<td>↓ *</td>
<td>↓ *</td>
<td>NS</td>
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Five trials have been published showing efficacy of UF in heart failure with the Aquadex system. Of these, 2 have been randomized controlled trials (RCT), and the remainder have been case series (CS). In these trials, the only finding/outcome supported statistically by >1 clinical trial was fluid removal. E indicates efficacy in achieving a particular goal; NA, data not available; NS, did not differ from control.

*P < 0.05.
substantial randomized controlled data on the safety and efficacy of UF and argues for a cautious approach to this therapy. The data available to ascertain safety and efficacy are derived principally from only 2 randomized controlled trials, which involved a total of 240 patients with ADHF during a single hospitalization. Although the findings from the UNLOAD trial are provocative, difficult questions remain to be answered regarding the appropriate use of UF in the setting of ADHF. An alternative explanation for the apparent benefits observed in the UF group may simply be that the diuretic group received less effective treatment, decongestion, and weight loss. Rehospitalization rates may not have differed had both treatments resulted in a similar degree of volume reduction.

The population of patients admitted with ADHF who are more likely to benefit from UF rather than diuretics is unclear from current clinical trial data. Patients enrolled in most of the UF trials reviewed earlier gained entry to these studies through a fairly liberal set of entry criteria. In UNLOAD, adult patients within 24 hours of admission need only to have exhibited 2 of the following signs of volume overload and congestion: (a) peripheral edema $\geq 2 +$; (b) jugular venous distension $> 7$ cm; (c) pulmonary edema or pleural effusion on chest radiograph; (d) enlarged liver or ascites; or (e) rales, paroxysmal nocturnal dyspnea or orthopnea. Exclusion criteria were more numerous and included among others (a) sCr $> 3.0$ mg/dL; (b) systolic blood pressure $< 90$ mm Hg; (c) IV vasopressors; (d) vasoactive drug use during or before hospitalization; (e) recent use of iodinated contrast; and (f) comorbidities expected to “prolong hospitalization.” No specific criteria were developed to select for or identify patients with CRS. The study population had an average sCr of 1.5 mg/dL (compared with 1.8 mg/dL in the Acute Decompensated Heart Failure National registry).3 Thus, virtually all UF trial subjects were hemodynamically stable with preserved systolic blood pressure and reasonably well-preserved renal function at the time of enrollment (the “wet” and “warm” clinical profile). This group (>70% to 80% of hospitalizations for ADHF) is generally easily decongested with diuretic therapy and has a low in-hospital mortality during conventional treatment. The UNLOAD patients seem to have had better renal function than the usual population admitted with ADHF, and it is not yet clear whether the decreased readmission rate can be extrapolated to the more typical and sicker hospitalized HF population.

The population of patients who are most likely to benefit from UF should be better defined. The costs associated with the introduction of any new technology must be carefully evaluated in the current era of cost containment and cost effectiveness analysis. The capital cost for each Aquadex console is approximately $25,000 and disposable supply costs run $900 for a single UF cassette.22 In contrast, the cost of a generic IV diuretic generally averages $< 5$ per day. The additional costs of UF could be justified if hospital LOS was shortened. However, this outcome has yet to be demonstrated in a randomized controlled trial. Although the end point of hospital readmission was decreased in the UF treatment group in UNLOAD, using UF in the ADHF patient group at greatest risk for readmission would seem to support better the economic case for treatment. However, strategies to prospectively identify this cohort successfully remain in evolution.16

Beyond decongestion through renal elimination of salt and water, diuretics may exert additional salutary effects including improved cardiovascular performance in acute and chronic HF and exert favorable effects of myocardial remodeling. IV furosemide administration results acutely in increased venous capacitance, which may be an important factor in acutely ameliorating the symptoms of dyspnea and congestion.23 Diuretics have also been shown to improve cardiac performance by decreasing afterload. Francis et al found an acute increase then decrease in systemic vascular resistance with bolus IV furosemide administration. Wilson et al found an increase in stroke volume and decrease in systemic vascular resistance after more chronic diuretic treatment for ADHF. Furthermore, the increased cardiac performance was correlated not with decreased preload resulting from salt and water loss but with lowered systemic vascular resistance. Although both diuretics and UF would be expected to improve preload and improve ventricular geometry in functional mitral regurgitation, the additional benefit of decreased afterload may also help reduce the regurgitant flow and improve forward cardiac output. Thus, direct vasoactive effects of diuretics (unrelated to their renal tubular activities) may play a role in the benefits obtained with pharmacological therapy.

Chronic administration of diuretics may also favorably affect myocardial remodeling by decreasing myocardial fibrosis. Torsemide (but not furosemide) has been shown to quantitatively reduce myocardial collagen content by endomyocardial biopsy and decrease circulating serum measures of type I collagen synthesis.26 There is also experimental evidence to suggest torsemide can decrease the profibrotic factor, aldosterone.27 However, it remains to be determined whether decreased myocardial fibrosis can result in improvement in diastolic function.

Although trials studying the impact of IV diuretics on survival in ADHF have not been performed, several studies have been performed using surrogate markers of clinical outcome in HF. For example, neurohumoral activation (eg, plasma endothelin-1, norepinephrine, and B-type natriuretic peptide) decreased rapidly after improvement in ventricular loading conditions produced by IV diuretics.28 Unlike loop diuretics, the ability of UF to acutely improve neurohormonal activation remains unproved and the magnitude of the effect (if indeed present) relative to diuretics is unknown. In patients who were acutely congested and in whom an elevated intra-abdominal pressure was measured, Mullens et al found a strong correlation between renal function and intra-abdominal pressure. In addition, the accepted efficacy and safety of IV diuretics were reflected in the 2009 update to the
ACC/AHA HF diagnosis and management guidelines, IV diuretics represented the only class I recommendation for ADHF. In the setting of inadequate relief of congestion with diuresis, the next recommendation is of intensified diuresis. UF received a class IIa recommendation, recognizing that it is reasonable to apply this therapy in refractory congestion but not as a first-line therapy, and that additional studies are needed to define the clinical situations where patients are most likely to benefit.

The potentially deleterious effects of diuretics have been used to argue for a role of UF in ADHF, but efforts are underway to delineate ways to minimize potential toxicities of loop diuretics. Recent data suggest the continuous infusion of loop diuretic results in better diuresis with less likelihood of a decrement in renal function as compared with the bolus diuretic approach that was used in all published UF trials. In fact, this hypothesis is now being tested within the National Heart, Lung, and Blood Institute–sponsored Heart Failure Network through the DOSE-AHF study. Thus, optimal pharmacological therapy with diuretics continues to evolve and now includes different administration strategies to produce more effective and potentially less toxic decongestion. A sub-study of the UNLOAD trial also argues that both diuretics and UF impact renal physiology similarly. No difference in net fluid removal at 24 hours was observed in this subgroup. Importantly, quantitative measures of renal blood flow, glomerular filtration rate, and filtration fraction did not differ between treatments suggesting that equivalent volume reduction results in equivalent effects on renal physiology and thus defined neither renal benefit nor harm to UF over conventional diuretics, in this small carefully selected population.

The potential for adverse effects and complications of UF therapy should also be considered. In particular, possible adverse renal effects needs to be better evaluated. In the UNLOAD study population, the mean rise in sCr experienced by the UF group at 72-hour approached 0.3 mg/dL compared with 0.15 mg/dL in the diuretic group. Although the increase in sCr did not achieve statistical significance, the acute deterioration in renal function during volume removal should raise concerns about long-term prognosis. The findings presented by Liang et al at the Mayo Clinic raise the specter that in a high-risk patient population (mean GFR of 38 mL/min, which was significantly worse than the UNLOAD population or that reported in either Acute Decompensated Heart Failure National or OPTIMIZE-HF) UF may not be the appropriate therapeutic choice for many patients. Thus, trials designed to define conditions when UF is safest should also be performed.

Other potential complications associated with UF should also be recognized (summarized in Table 1). The relatively slow rate of blood flow achieved in the venovenous circuit can result in filter thrombosis and the need for replacement filters to complete treatment, raising the ultimate cost of UF. To prevent filter thrombosis, systemic anticoagulation with unfractionated heparin or an alternative is required. In addition to increasing bleeding risk, anticoagulation requires additional monitoring of aPTT or ACT. In practice, venous access is often problematic with standard peripheral IV access, requiring the use of a specialized midline type catheter or even a central venous line at increased cost and potential risk. Allergic reactions to similar devices have also been described.

Apart from efficacy in volume loss and decreased readmission rate, clinical trial experience with the Aquadex system has not identified end points that are consistently improved across published studies (Table 2). Surprisingly, the symptom-derived measurements at the 48-hour assessment point in UNLOAD did not differ significantly between the UF and diuretic groups, and the weight loss metric was not different between the UF and standard diuretic cohorts in the RAPID-CHF study. The absence of reproducible outcomes across clinical studies is likely multifactorial, representing the relatively small patient populations in each study and differences in approach (ie, intermittent UF at a high rate of volume removal versus a slower continuous rate of withdrawal) to volume removal in each trial. These inconsistencies highlight not only the need to perform additional, larger randomized studies to identify consistent clinical end points but also to study whether the optimal strategy for UF is intermittent or slow continuous removal of fluid. In an attempt to define the safety and efficacy of UF in CRS, the National Heart, Lung, and Blood Institute Heart Failure Network and CHF Solutions, Inc, are currently conducting the Cardiorenal Rescue Study in acute decompensated heart failure. This multicenter, randomized controlled study aims to enroll 200 people in a 1:1 comparison between peripheral UF and standard diuretic therapy. The primary end point is a composite of weight loss and sCr, with numerous prespecified secondary outcome metrics. Completion of this study will help provide key clinical information regarding the specific application of UF in patients with CRS.

Finally, as new therapies for HF emerge, the end points with which clinical success is measured should be resolved with greater clarity. It is becoming increasingly apparent that treatment strategies, which improve symptoms during a hospitalization for ADHF, do not necessarily translate in long-term therapeutic success. Tolvaptan, a selective V2-receptor antagonist, has been shown to decrease symptoms of dyspnea, improve hyponatremia, and promote more effective weight loss than an IV loop diuretic alone during HF hospitalization. However, the recently completed EVEREST trial failed to demonstrate long-term benefits on mortality or other secondary end points. Although the mechanisms of action of UF and vasopressin inhibition differ, the long-term outcomes of any new pharmacological or device-based therapy must be validated or refuted based on data from randomized, controlled trials. It is possible the short-term (90 days) reduction in HF rehospitalizations observed in UNLOAD may not be sustained or, worse, could be associated with adverse effects on long-term mortality. Although lower re-
hospitalization rates are highly desirable, the standard assessment of any new therapeutic must be its effect on mortality. Thus, a well-designed and sufficiently powered outcome trial of UF is needed before this approach should be considered for generalized management of ADHF.

Conclusion
On the basis of a critical review of the limited data available in 2009, UF has not consistently demonstrated superiority over aggressive IV diuretic therapy in improving symptoms, weight loss, or preservation of renal function and encumbers the potential for additional complications. Proposed benefits such as improved diuretic responsiveness after UF therapy have not been rigorously tested. Significant questions remain regarding the specific populations of patients most likely to benefit from this expensive therapy and those in whom it should be avoided. Finally, the optimal strategy (ie, intermittent versus continuous) for fluid removal by peripheral UF has yet to be determined. UF represents a promising technology, which will likely find a place in the armamentarium of therapies for HF. Additional randomized-controlled studies with larger numbers of patients over a broader range of illness are needed. However, until these questions can be answered, UF should not supplant diuretics as first-line therapy for routine patients presenting with ADHF.

Acknowledgments
We thank Paul Arpino, PharmD, for providing pricing information on IV diuretics.

Sources of Funding
Dr Shin has received consulting fees from CHF Solutions and receives research funding from the National Institutes of Health.

Disclosures
None.

References
Response to Shin and Dec

Bradley A. Bart, MD

After more than 40 years of loop diuretics, death and rehospitalization rates for patients with acute decompensated heart failure remain unacceptably high. The addition of inotropes, vasodilators, natriuretic peptides, adenosine antagonists, arginine vasopressin antagonists, and invasive hemodynamic monitoring have done nothing to improve outcomes in this patient population. Ongoing faith in this pharmacological alchemy is dangerous testament to what is considered expert opinion. Researchers have known for more than 100 years that sodium is the major determinant of extracellular fluid volume in heart failure. Excess total body sodium is the primary treatment target for hospitalized patients suffering from sodium/volume overload. Loop diuretics, although often effective in removing water, are inherently incapable of predictably reducing total body sodium, whereas ultrafiltration predictably reduces total body sodium in all treatments. Treatment with diuretics may be better than doing nothing, but in controlled trials, ultrafiltration is superior to diuretics with respect to sodium removal, water removal, and rehospitalization rates. Ultrafiltration should be the standard of care for patients with sodium/fluid overload admitted to the hospital with acute decompensated heart failure—other promising therapies should prove safety and efficacy against the standard of ultrafiltration. The ongoing endorsement of diuretics as first-line treatment for sodium/volume overload in the acute decompensated heart failure guidelines pays homage to tradition but ignores new knowledge of the failings and safety concerns of diuretics. With 3-month rehospitalization rates as high as 30%, our patients can no longer afford to suffer from the inertia that resists the use of ultrafiltration—the most effective and reliable method of reducing total body sodium.
Ultrafiltration Should Not Replace Diuretics for the Initial Treatment of Acute Decompensated Heart Failure
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Circ Heart Fail. 2009;2:505-511
doi: 10.1161/CIRCHEARTFAILURE.109.862474
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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