The Role of Early and Sufficient Isolated Venovenous Ultrafiltration in Heart Failure Patients With Pulmonary and Systemic Congestion

Maria Rosa Costanzo, MD, FAHA, FACC,[1] L.S. Chawla, MD,[2] J.A. Tumlin, MD,[3] C.A. Herzog, MD, FAHA, FACC[4] Peter A. McCullough, MD, MPH, FACC, FACP, FAHA, FCCP, FN,[5] J.A. Kellum, MD, FACP, MCCM[6] C. Ronco, MD[7]

[1]Midwest Heart Specialists-Advocate Medical Group, Naperville, IL; [2]Department of Medicine, Division of Renal Diseases and Hypertension, George Washington University Medical Center, Washington, DC; [3]University of Tennessee College of Medicine, Department of Internal Medicine, Chattanooga, TN, [4]Department of Medicine, Division of Cardiology, Hennepin County Medical Center, University of Minnesota, Minneapolis, MN; [5]St. John Providence Health System, Warren, MI, Providence Hospitals and Medical Centers, Southfield and Novi, MI; [6]Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA; [7]Department of Nephrology Dialysis & Transplantation, San Bortolo Hospital, Vicenza, Italy

Hypervolemia, present in at least 70% of patients with decompensated heart failure, results in renal dysfunction due to increased renal venous pressure, impaired renal autoregulation, and decreased renal blood flow that are associated with increased morbidity and mortality. Loop diuretics, widely used in congested patients, result in the production of hypotonic urine and neurohormonal activation. In contrast, ultrafiltration (UF) removes isotonic fluid without increasing renin secretion by the macula densa. Simplified devices that permit us to perform UF with peripheral venous access, adjustable blood flows, and small extracorporeal blood volumes make this therapy feasible at most hospitals and in less acute care settings. Conflicting results on the effects of UF in heart failure patients underscore the challenges of patient selection and choice of fluid removal rates. Unfavorable outcomes in patients undergoing UF in the midst of cardiorenal syndrome type 1 are in contrast with the sustained benefits of UF initiated before unsuccessful use of high-dose intravenous (IV) diuretics. UF rates should be based on a precise knowledge of the degree of hypervolemia and careful assessment of blood volume changes, so that extracellular fluid gradually refills the intravascular space and volume depletion is avoided. Poor outcomes are likely to occur if fluid removal rates are not tailored to individual patients' clinical characteristics. A large trial is ongoing to determine if a strategy of early UF, initiated before renal function is worsened by other therapies, is superior to IV diuretics in reducing 90-day heart–failure–related hospitalizations in patients with pulmonary and systemic congestion.

[Rev Cardiovasc Med. *2013;14(2-4):e123-e133 doi:10.3909/ricm0685]*

KEY WORDS

Heart failure • Cardiorenal syndrome • Ultrafiltration • Diuretics

It is estimated that at least 70% of patients hospitalized with acute decompensated heart failure (ADHF) have pulmonary and/or venous congestion.[1,2] Among these hypervolemic patients, cardiac output (CO) is normal or decreased in approximately 50% and 20% of patients, respectively. Congestion with preserved CO may result in increased renal venous pressure and impaired renal autoregulation, whereas congestion with reduced CO may be associated with both increased renal venous pressure and decreased renal blood flow.[3] These hemodynamic abnormalities contribute to the impairment of kidney function observed in at least 30% of ADHF patients.[4] Therefore, it is not surprising that ADHF patients with congestion (defined by the presence of dyspnea, jugular vein distention, and edema that persists after initial hospital therapy) have a twofold increase in 60-day mortality compared with patients without congestion.[5] Loop diuretics, used in approximately 90% of ADHF patients, inhibit the $Na^+2Cl^-K^+$-cotransporter, NKCC2, expressed in the thick ascending limb of the loop of Henle of the nephron. This cotransporter is also responsible for the sensing of sodium in the macula densa, which is located at the end of the thick ascending limb. By inhibiting sodium transport to the macula densa, loop diuretics create a situation analogous to low sodium delivery to the macula densa, thus eliciting its secretion of renin.[3,6] Thus, the very mechanism of action of loop diuretics results in stimulation of renin release and activation of the renin-angiotensin-aldosterone system (RAAS), a pivotal driver of heart failure development and progression. Data from the Diuretic Optimization Strategies Evaluation (DOSE) trial show that 42% of ADHF patients reached the composite endpoint of death, rehospitalization, or emergency department visit at 60 days regardless of whether loop diuretics were administered at low versus high doses or by bolus injection versus continuous infusion.[7]

These outcomes highlight the fact that there are unmet therapeutic needs for a subset of ADHF patients at risk of developing the acute cardiorenal syndrome (CRS) type 1, that justify the interest in exploring the role of alternative methods of fluid removal, such as isolated venovenous ultrafiltration (UF), in this population (Table 1).[8,9]

The implementation of UF in ADHF patients has been facilitated by the introduction of simplified devices that permit us to perform UF with peripheral venous access, adjustable blood flow, and small extracorporeal blood volumes, making UF feasible at most hospitals and in less acute care settings (Figure 1).[10] In 2002, the Aquadex System 100 peripheral venovenous system (Gambro UF Solutions, Minneapolis, MN) was approved by the US Food and Drug Administration (FDA) for clinical use based on the results of the Simple Access Fluid Extraction (SAFE) trial.[10] This study showed that, in 21 fluid-overloaded ADHF patients, the removal of an average of 2600 mL of ultrafiltrate during an 8-hour treatment period resulted in a mean weight loss of approximately 3 kg without changes in heart rate, blood pressure, serum creatinine (sCr), and electrolytes, or the occurrence of major adverse events. The UF studies conducted

The implementation of UF in ADHF patients has been facilitated by the introduction of simplified devices that permit us to perform UF with peripheral venous access, adjustable blood flow, and small extracorporeal blood volumes, making UF feasible at most hospitals and in less acute care settings.

TABLE 1

Differences Between Loop Diuretics and Ultrafiltration

Diuretics	Ultrafiltration
Elimination of hypotonic urine	Removal of isotonic plasma water
Development of diuretic resistance and lack of dosing guidelines	Precise control of rate and amount of fluid removal
Reduced glomerular filtration rate	Unchanged glomerular filtration rate
Direct neurohormonal activation	No direct neurohormonal activation
Electrolyte abnormalities	No effect on plasma concentration of electrolytes

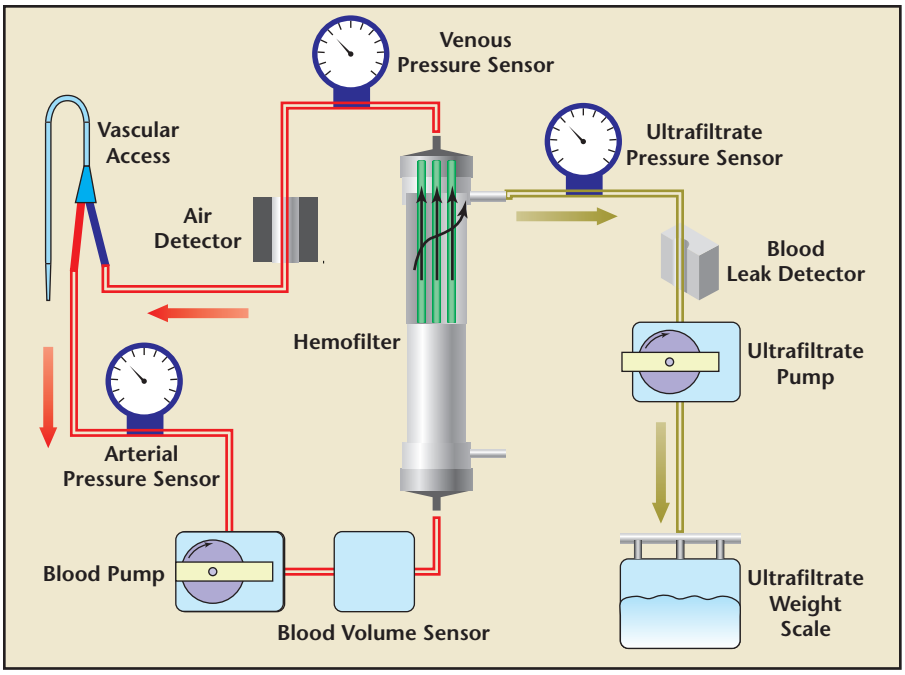


Figure 1. In a contemporary ultrafiltration device, the console controls blood removal rates and extracts ultrafiltrate at a maximum rate set by the treating physician. Blood is withdrawn from a vein through the withdrawal catheter (*red*). Tubing connects the withdrawal catheter to the blood pump. Blood passes through the withdrawal pressure sensor just before it enters the blood pump tubing loop. After exiting the blood pump, blood passes through the air detector and enters the hemofilter (made of a bundle of hollow fibers) through a port on the bottom, exits through the port at the top of the filter, and passes through the infusion pressure sensor before returning to the patient (*blue*). Ultrafiltrate sequentially passes through the ultrafiltrate pressure sensor, the ultrafiltrate pump, and the collecting bag that is suspended from the weight scale. A hematocrit sensor is located on the withdrawal line.

after the SAFE trial were discussed at the 11th Acute Dialysis Quality Initiative (ADQI) meeting, which was convened to focus on the CRS.[11] A detailed report of the ADQI process has been published previously.[12]

Pilot Studies

One pilot study sought to determine if UF begun within 12 hours of admission safely restores euvolemia, permits discharge in ≤ 3 days, and prevents 90-day rehospitalization in 20 ADHF patients with diuretic resistance (defined as sCr ≥ 1.5 mg/dL combined with daily oral furosemide doses ≥ 80 mg or equivalent doses of other loop diuretics).[13] Vasoactive drugs and more than one dose of intravenous (IV) loop diuretic were prohibited prior to initiation of UF. An average of 8654 ± 4205 mL was removed with 2.6 ± 1.2 8-hour UF courses. Twelve patients (60%) were discharged in ≤ 3 days. One patient was readmitted in 30 days and two patients in 90 days. Improvement in weight ($P = .006$), Minnesota Living with Heart Failure scores ($P = .003$), and Global Assessment ($P = .00003$) observed after UF persisted at 30 and 90 days. Levels of B-type natriuretic peptide (BNP) were decreased after UF (from 1236 ± 747 pg/mL to 988 ± 847 pg/mL) and at 30 days (816 ± 494 pg/mL) ($P = .03$). Blood pressure, renal function, and medications were unchanged.[13]

Notably, in seven patients with hyponatremia (serum sodium ≤ 135 mg/dL), sodium increased from pretreatment values both at discharge ($P = .042$) and at 90 days ($P = .017$). Because ultrafiltrate is isotonic with plasma, the rise in serum sodium cannot be attributed to direct effects of UF, but rather to attenuation of neurohormonal activation, as indicated by the drop in plasma BNP levels without worsening renal function.[14]

The results of this study suggest that, in ADHF patients with fluid overload and diuretic resistance, UF initiated before therapy with IV loop diuretics effectively and safely decreases length of hospitalization and readmissions with clinical benefits still present at 90 days.[13]

This study was a preliminary evaluation of UF in ADHF patients and as such it has important limitations, including a small sample size, lack of a control group, and the now-obsolete FDA-mandated restriction of each UF course to 8 hours.

Nevertheless, the observed benefits may be due to the fact that fluid removal by UF occurred before upregulation of neurohormonal activity by IV loop diuretics.[14] In the Relief of Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure (RAPID-CHF) trial, 40 patients were randomized to either a single 8-hour course of UF at fluid removal rates determined by the treating physician plus usual care, or to usual care alone.[15] Median time from consent to initiation of UF was 3.9 hours. Weight loss, the primary endpoint of the study, failed to reach statistical significance ($P = .240$). However, compared with the usual care group, UF-treated patients had greater net fluid loss at 24 hours (4650 mL vs 2838 mL; $P = .001$) and at 48 hours (8145 mL vs 5375 mL; $P = .012$), and greater 48-hour improvement in dyspnea ($P = .039$) and other heart failure symptoms ($P = .023$). Usual care and UF were similar in terms of renal function, electrolytes, heart rate, systolic blood pressure, and duration of the index hospitalization. Compared with the usual care group, patients receiving UF had a slight but statistically significant drop in hemoglobin at 48 hours (+ 0.55 g/dL vs −0.4 g/dL; $P = .004$), a difference that was transient and not associated with detectable bleeding. Use of heparin and retention of

blood in the UF circuit may explain this finding.[15]

As in the previous study, effective decongestion and clinical improvement were observed with early initiation of UF, before further elevation of sCr levels resulting from large IV loop diuretic doses.[8,13-15] The results, however, must be interpreted with caution, given the small sample size and lack of assessment of outcomes beyond 48 hours.[15]

A single-center report on the use of UF in 11 patients defined by the investigators as having "very advanced, diuretic-resistant heart failure" deserves special attention due to the valuable lessons it provides on the appropriate utilization of UF in ADHF patients.[16] The study population had a pretreatment sCr of 2.2 mg/dL, mean estimated glomerular filtration rate (eGFR) of 38 mL/min (with 6/11 having eGFR $<$ 30 mL/min), and included nine patients (82%) with documented severe right ventricular (RV) dysfunction and three patients (27%) with pericardial constriction. Prior to UF, mean daily IV furosemide dose was 258 mg and seven patients (64%) also received metolazone. The study goal to remove 4 L of fluid with each 8-hour UF course was achieved in 13 of 32 treatments (41%). Five patients (45%) experienced an increase in sCr $>$ 0.3 mg/dL and five patients required hemodialysis (HD). Interestingly, two of the five patients that ultimately required HD for "persistent diuretic-resistant volume overload or uremic symptoms" did not have an increase in sCr with UF. There was no obvious correlation between amounts of fluid removed by UF and the need for HD.[16] The extreme severity of illness of these patients is underscored by the 55% 6-month mortality. Such mortality rate identical to that occurring in the medical therapy arm of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, and it exceeds the 6-month mortality ever reported in any other a heart failure clinical trial.[17] Based on these observations, several messages clearly emerge for this single center case series: (1) isolated venovenous UF does not significantly alter the outcomes of patients with end-stage heart failure and should be used with extreme caution in this patient population, and (2) fast fluid removal rates are particularly detrimental in patients with RV dysfunction who are exquisitely susceptible to intravascular hypovolemia due to the storage of a larger proportion of blood in the venous circulation. Thus, overly aggressive UF in heart failure patients with RV dysfunction can rapidly decrease renal perfusion pressure, cause a rise in sCr, and convert nonoliguric renal dysfunction into oliguric failure and dialysis dependence[16,18,19]; high doses of IV loop diuretics prior to UF, by intensifying neurohormonal activation, may predispose the kidney to injury by additional fluid removal with UF.

. . . overly aggressive UF in heart failure patients with RV dysfunction can rapidly decrease renal perfusion pressure, cause a rise in sCr, and convert nonoliguric renal dysfunction into oliguric failure and dialysis dependence.

The UF Versus IV Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure Trial

The specific aim of the Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) trial was to compare the safety and efficacy of an early strategy of UF versus standard IV diuretic therapy in ADHF patients with two or more easily detectable signs of congestion. To achieve this goal, randomization had to occur within 24 hours of hospital admission and a maximum of two IV loop diuretic doses were permitted before randomization.[20] A total of 200 patients (aged 63 $\pm$ 15 years; 69% men; 71% ejection fraction $\leq$ 40%) were randomized to UF or IV diuretics. At 48 hours, weight (5.0 $\pm$ 3.1 kg vs 3.1 $\pm$ 3.5 kg; P = .001) and net fluid loss (4.6 L vs 3.3 L; P = .001) were greater in the UF group.[20] Dyspnea was similarly improved in the two groups. At 90 days, the UF group had fewer patients rehospitalized for heart failure (18% vs 32%; P = .037), and unscheduled visits for worsening heart failure (21% vs 44%; P = .009). A larger net fluid loss with UF did not shorten the length of the index hospitalization. However, duration of hospitalization is often determined by multiple factors, some of which are unrelated to patients' response to therapy, including adjustment of heart failure therapy before discharge, performance of additional diagnostic and therapeutic procedures, treatment of comorbidities, social issues related to placement of patients after discharge, and lack of well-defined criteria for hospital discharge.[21] The percentage of patients with increases in sCr levels $>$ 0.3 mg/dL was similar in the UF and standard care group at 24 hours (14.4% vs 7.7%; P = .528), at 48 hours (26.5% vs 20.3%; P = .430), and throughout the 90-day follow-up period.[20] Occurrences of hypokalemia (serum potassium $<$ 3.5 mEq/L) were fewer in the UF than in the diuretic group (1% vs 12%; P = .018). In both groups, episodes of hypotension

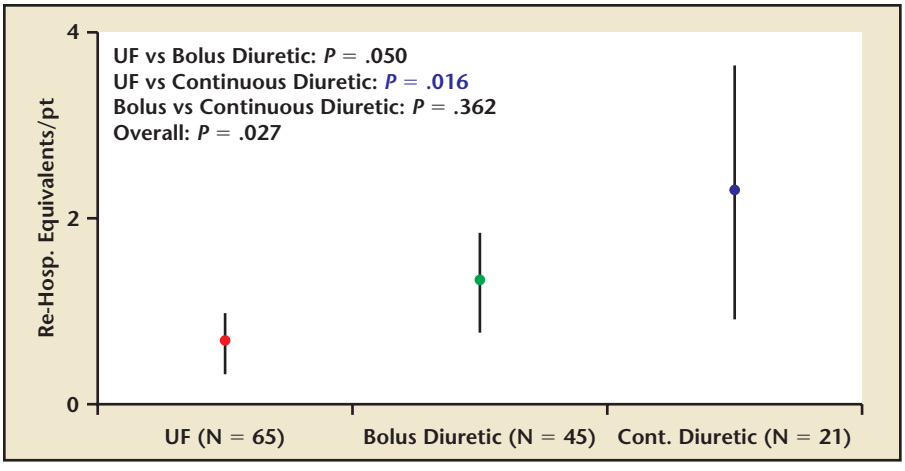
during treatment were rare (4% vs 3%).[20] Complications specifically related to UF included clotting of five filters, one catheter infection, and the requirement for HD in one patient deemed to have congestion refractory to UF.[20]

The UNLOAD trial lacked treatment targets, blood volume assessments, and cost analysis. These limitations, however, do not weaken the key findings of this trial: an early strategy of UF, initiated before the administration of high-dose IV diuretics, effectively reduces congestion and 90-day heart-failure–related rehospitalizations in ADHF patients. These outcomes are at least partially explained by a post hoc analysis from the UNLOAD trial in which the outcomes of 100 patients treated with UF were compared with those of 100 control group subjects divided according to whether they had received IV diuretics by continuous infusion (n = 32) or bolus injections (n = 68).[22] Despite similar amounts of fluid removed by UF and continuous IV diuretic infusion, at 90 days, heart-failure–related rehospitalizations plus unscheduled visits (rehospitalization equivalents) were fewer in the UF group than in continuous IV diuretic infusion group ($P = .016$) (Figure 2).[22] Volume overload in HF patients is inevitably related to an increase and abnormal distribution of total body sodium.[23] The simultaneous reduction of total body sodium and excess fluid by UF may be more effective than removal of hypotonic fluid by diuretics or free water by vasopressin V_2 receptor blockers.[23,24] It is also possible that prehospitalization diuretic use itself reduces the natriuresis achievable with the subsequent administration of IV loop diuretics.[25]

. . . an early strategy of UF, initiated before the administration of high-dose IV diuretics, effectively reduces congestion and 90-day heart-failure–related rehospitalizations in ADHF patients.

Increased central venous pressure (CVP) is independently associated with worsening renal function.[26] The increased amounts of sodium and water reabsorbed by the kidney due to neurohormonal upregulation predominantly fill the compliant venous circulation, increasing CVP. Transmission of venous congestion to the renal veins further impairs GFR.[14,27,28] If fluid is removed by UF at rates that do not exceed the interstitial fluid mobilization (plasma refill) rate of 14 to 15 mL/min, CVP may be lowered without the neurohormonal activation that inescapably occurs when IV loop diuretics inhibit transport of sodium to the macula densa.[27,28]

Figure 2. Mean rehospitalization equivalents (rehospitalization + unscheduled office and emergency department visits for heart failure) in the ultrafiltration (UF; *red circle*), intravenous (IV) bolus diuretic (*green circle*), and IV continuous diuretic (*blue circle*) groups; *P* values are for the comparison between UF and IV bolus diuretic, UF and IV continuous diuretic, IV bolus diuretic, and IV continuous diuretic. Error bars indicate 95% confidence interval. Reprinted with permission from Costanzo MR et al.[22]



The Cardiorenal Rescue Study in Acute Decompensated Heart Failure Trial

In sharp contrast to UNLOAD, which compared an early strategy of UF versus IV loop diuretics, the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial compared the effects of UF, delivered at a fixed rate of 200 mL/h, with those of stepped pharmacologic therapy (SPT; inclusive of adjustable doses of IV loop diuretics, thiazide diuretics, vasodilators, and inotropes) in ADHF patients who had experienced an increase in sCr anywhere between 12 weeks before and 7 days after admission despite escalating doses of diuretics.[29] Thus, by study design, all subjects were in the midst of the CRS type 1 with an acute rise in sCr at the time of randomization. The primary endpoint of CARRESS-HF was the bivariate change from baseline in sCr level and body weight, as assessed 96 hours after randomization.[30] The selection of this primary endpoint was based on the assumptions that weight loss is a measure of successful volume reduction, whereas an increase in sCr is always an adverse outcome of decongestive therapies. In the patient population of CARRESS-HF, UF was inferior to SPT with respect to the 96-hour

bivariate endpoint owing primarily to an increase in sCr level in the UF group (+ 0.23 ± 0.70 mg/dL for UF vs −0.04 ± 0.53 mg/dL for SPT; $P = .003$) without significant differences between groups in weight loss (−5.5 ± 5.1 kg for UF vs 5.7 ± 3.9 kg for SPT; $P = .58$). Furthermore, a higher percentage of patients in the UF group than in the SPT group had serious adverse events (72% vs 57%; $P = .03$), attributable mainly to higher incidences of kidney failure, bleeding events, and IV catheter–related complications.[29] Many aspects of both design and results of CARRESS-HF deserve thoughtful reflection. The simultaneous consideration of changes in sCr and weight is problematic. Among ADHF patients, transient minor increases in sCr may not necessarily reflect acute kidney injury (AKI) or adverse long-term prognosis. Among 336 patients enrolled in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, hemoconcentration (defined by increases in hematocrit, albumin, or total protein) after decongestive therapy was strongly associated with worsening renal function, defined as a ≥ 20% decrease in eGFR. However, despite a higher incidence of this small change in renal function from intense diuresis, patients with hemoconcentration had significantly lower 180-day mortality (hazard ratio, 0.31; $P = .013$).[31] Thus, aggressive decongestion of ADHF patients does not worsen outcomes provided that the resulting increases in sCr remain within the biologic variability of measurement (< 25% change). Interestingly, in a retrospective comparison of 25 UF-, 25 IV diuretics- and 25 nesiritide-treated patients, those treated with UF had the greatest increase in blood urea nitrogen, sCr, and number of patients with sCr increases > 0.5 mg/dL (44% UF vs 24% IV diuretics vs 20% nesiritide). Despite the unfavorable renal outcomes, all-cause 30-day rehospitalizations were fewer in the UF-treated patients than in those treated with either IV diuretics or nesiritide (12% UF vs 24% IV diuretics vs 28% nesiritide).[32] Data from the UNLOAD trial also show that, regardless of assignment to UF or IV diuretics groups, the patients who had the greatest increases in sCr during treatment had the fewest heart-failure–related hospitalizations at 90 days (MR Costanzo, personal communication, 2007). Finally, in the DOSE trial, compared with the low-dose IV diuretic group, the high-dose group had simultaneously greater net fluid loss ($P = .001$) and a higher percentage of patients with a sCr increase > 0.3 mg/dL (23% vs 14%; $P = .04$) at 72 hours, which did not translate into a higher rate of cardiovascular events at 60 days.[7] Thus, transient increases in sCr resulting from decongestive therapies are not always predictive of adverse long-term outcomes, as they may only be indicative of temporary hemoconcentration. In CARRESS-HF, the rate of fluid removal was mandated to be the same (200 mL/h) in all patients assigned to the UF arm and no adjustments were allowed according to patients' hemodynamics or renal function. This fluid removal rate may be inadequate for some patients, as suggested by the lack of difference in weight loss between the two groups at the 96-hour assessment.[29] On the other hand, a UF rate of 200 mL/h may be excessively fast for patients with a lower blood pressure and/or RV dysfunction and may have resulted in worsening renal function due to intravascular volume depletion. Although no information is available on the incidence and severity of RV dysfunction in the CARRESS-HF population, it is important to repeat that RV dysfunction increases the risk of intravascular depletion with fluid removal because a larger proportion of the blood volume is stored in the venous circulation.[16,33,34] Clinical experience shows that, regardless of the method used to decongest ADHF patients, removal of fluid must be tailored to individual patients, with careful consideration of their blood pressure, renal function variables, body mass, and urine output. Review of the design manuscript of the CARRESS trial reveals that in the SPT group a careful treatment algorithm provided for ongoing adjustments of IV diuretic doses and for the use of thiazide diuretics, vasodilators, and inotropic drugs based on the individual patient's blood pressure and urine output.[30] The benefits of flexible therapy were not extended to patients in the UF group. Although the reasons for this discrepancy remain unexplained, it is important to note that contemporary UF devices are equipped with hematocrit sensors for the estimation of blood volume. In clinical practice thresholds of hematocrit, changes can be established for each patient to ensure that the pace of fluid removal does not exceed the capillary refill rate so that intravascular volume depletion can be prevented.[35]

Clinical experience shows that, regardless of the method used to decongest ADHF patients, removal of fluid must be tailored to individual patients, with careful consideration of their blood pressure, renal function variables, body mass, and urine output.

In the CARRESS-HF trial, the use of vasodilators or positive inotropic

agents was prohibited in the UF group unless deemed necessary for rescue therapy. In contrast, vasoactive drugs were included in the SPT algorithm and 12% of patients in this treatment arm received inotropes before the 96-hour assessment.[29] In these patients, use of positive inotropic agents may have prevented or attenuated worsening renal function resulting from a lower blood pressure.

Other aspects of the CARRESS-HF study should be considered in interpreting the trial's results. In addition to a 20% crossover rate in the study, there were 36 patients in the UF group (39%) who also received IV diuretics. Of these, 8 UF patients (9%) received IV diuretics instead of UF and 28 UF patients (30%) also received IV diuretics before the 96-hour assessment.[29] Based on the high percentage of UF patients that also received IV diuretics, the observed greater rise in sCr cannot be attributed solely to mechanical fluid removal.

Finally, the increase in sCr level of at least 0.3 mg/dL required for enrollment in the CARRESS-HF trial could have occurred anywhere between 12 weeks before and 10 days after the index admission for ADHF. Data on whether the average duration of worsening renal function was comparable in the two groups are not provided. Knowledge of this variable is very important, given the large body of experimental and clinical evidence that both severity and duration of underlying renal dysfunction are key risk factors for the development of AKI.[36] Thus, CARRESS-HF was not a prevention trial, but a treatment trial of the CRS type 1. Recent data suggest that worsening renal function during treatment of ADHF may indicate underlying impairment of renal reserve rather than a consequence of treatment.[37] The outcomes of the CARRESS-HF population were very poor, regardless of fluid removal method or degree of weight loss, as indicated by the fact that only one-tenth of the patients had sufficient decongestion at 96 hours and more than 30% died or were readmitted for ADHF within 60 days of the index hospitalization.[29,37]

Selection of Potential Candidates for UF

The conflicting results on the effects of UF as a method for fluid removal in ADHF patients highlight the importance of patient selection and choice of fluid removal targets. Practice guidelines recommend that an inadequate response to an initial dose of IV loop diuretic be treated with an increased dose of the same drug.[1,38] If this measure is not effective, invasive hemodynamic assessment is recommended. Objective evidence of persistent congestion can then be treated with the addition of a thiazide diuretic, an aldosterone antagonist, or the use of continuous IV infusion of a loop diuretic. If all of these measures fail, mechanical fluid removal can be considered.[38] The degree of resistance to medical therapy that should be demonstrated before consideration of UF is alarmingly similar to that required for enrollment in the CARRESS-HF trial. However, the unfavorable outcomes in this patient population, which are in sharp contrast to the sustained benefits observed in the UNLOAD trial, suggest that initiation of UF in ADHF patients before they fail high-dose IV diuretics is a strategy that is both safer and more effective.[13,15,16,20,22,29,33-35]

Due to the potential complications and cost of UF therapy, it should not be used indiscriminately in all ADHF patients. For example, in patients with de novo heart failure or those not receiving daily diuretic therapy, fluid overload can be rapidly eliminated with IV diuretics; therefore, these drugs should be used instead of or before UF is considered. A more challenging clinical question is which patients who develop ADHF despite daily oral diuretic doses should be considered for early UF rather than IV diuretics.

Among 15 patients with ADHF who first received IV diuretics and were subsequently treated with UF due to refractory congestion, the urine sodium concentration in response to IV furosemide given before initiation of UF was significantly less than the sodium concentration in the ultrafiltrate after 8 hours of UF (60 ± 47 mmol/L vs 134 ± 8.0 mmol/L; $P = .000025$).[23] These results show that urinary sodium concentration in response to IV loop diuretics is not only lower than the sodium concentration in the ultrafiltrate, but highly variable between patients. In the same study no correlation was found between urinary sodium concentration and baseline renal function, which underscores the difficulty in predicting the natriuretic response of individual patients to a given dose of IV diuretic. Although it is plausible that UF may be especially effective in patients whose urinary sodium concentration is low after receiving a dose of IV loop diuretics, this hypothesis should be tested in prospective, randomized clinical trials.

A recent consensus statement proposes that congestion be graded according to a combination of clinical and laboratory parameters. The expert consensus suggests that a congestion grade > 12 together with low urine output (< 1000 mL/24 h) should trigger the use of extracorporeal fluid removal because, in patients with this degree of congestion, diuretics

are less likely to effectively reduce fluid overload.[39] This recommendation should also be prospectively validated.

Fluid Removal Targets and Monitoring of UF Therapy

The safety and efficacy of UF depend on the ability to remove fluid without causing hemodynamic instability and/or AKI. To achieve this goal, the amount and rate of fluid removal must be clearly established. If UF rates are too high, hemodynamic instability occurs because the refilling of the intravascular space from the interstitium cannot keep pace with the reduction in intravascular volume resulting from fluid withdrawal. In practice, UF should initially be prescribed at low rates (100-200 mL/h). After assessment of the hemodynamic response to UF, higher fluid removal rates can be tried in the absence of symptomatic hypotension and/or worsening renal function.[35] Rates of UF exceeding 250 mL/h are no longer recommended in patients with ADHF. Patients with predominantly right-sided heart failure or patients with heart failure and preserved systolic function are exquisitely susceptible to intravascular volume depletion and may only tolerate UF rates < 150 mL/h.[35] Clinical experience has shown that extracorporeal fluid removal is better tolerated when conducted with low UF rates over prolonged periods of time (> 8 h and up to 72 h). Unfortunately, in most studies conducted thus far, UF has been used only for short periods of time (≤ 40 h). Thus, the benefits of UF initiated before the onset of the CRS type 1 and performed with low fluid removal rates for > 40 hours deserves further investigation. A frequently used practical approach is to estimate fluid excess by comparing the patient's current weight with that measured in the absence of signs and symptoms of congestion, and remove at least 60% to 80% of this excess fluid without causing hemodynamic instability or worsening renal function. It is reasonable to define resolution of congestion as a jugular venous pressure ≤ 8 cm, absence of pulmonary rales, and trace or no edema.[35]

A substantial body of experimental and clinical evidence shows that increased CVP results in renal venous hypertension, which impairs renal function through multiple pathophysiologic mechanisms, including reduced transglomerular pressure, elevated renal interstitial pressure, myogenic and neural reflexes, baroreceptor stimulation, activation of sympathetic nervous system and RAAS, and inflammation.[3,27,28] Several small studies have shown that, in patients with heart failure, UF can reduce CVP independently from changes in CO and, unlike IV diuretics, without significant neurohormonal activation.[40] Larger prospective, controlled clinical trials are needed to definitively establish if fluid removal goals by UF might best be directed toward CVP rather than other clinical or hemodynamic variables. In lieu of invasive measurements of CVP, ultrasonography may permit us to estimate cardiac filling pressures with the assessment of the respiratory excursions of the diameter of the inferior vena cava (IVC). One study of intensive care unit patients undergoing continuous invasive monitoring of the CVP showed a moderate correlation ($r = -0.31$) of the IVC collapsibility index with CVP.[41] Although ultrasonography is noninvasive and inexpensive, its reliability strictly depends on the operator's skill and the patient's respiratory effort.[41]

Rates of UF exceeding 250 mL/h are no longer recommended in patients with ADHF.

Blood Volume Estimation

Theoretically, if UF is within the plasma refill rate, there shouldn't be a difference between pre- and posttreatment hematocrit values. Several on-line hematocrit sensors (Crit-Line, Hemametrics, Salt Lake City, UT; Hemoscan, Gambro, Lund, Sweden; Dedyca, Bellco, Mirandola, Italy) permit continuous estimation of blood volume changes during UF. These sensors can be programmed so that fluid removal is stopped if the increase in hematocrit exceeds the threshold set by the treating physician (3%-7%) and resumed when the hematocrit value falls below the prespecified limit, which indicates that adequate refilling of the intravascular volume from the interstitial space has occurred (Figure 3).[42] However, because numerous factors (including change in body position) can significantly alter hematocrit values, physical and laboratory assessments should also be considered to determine the appropriate UF rates and the amount of fluid that should be removed.

Biomarkers

Natriuretic peptides (NPs) have become important tools in the diagnosis, treatment, and prognostic assessment of patients with heart failure.[43] Studies in ADHF patients have shown that, although a drop in NP level in response to treatment is important, discharge BNP levels < 350 to 400 pg/mL

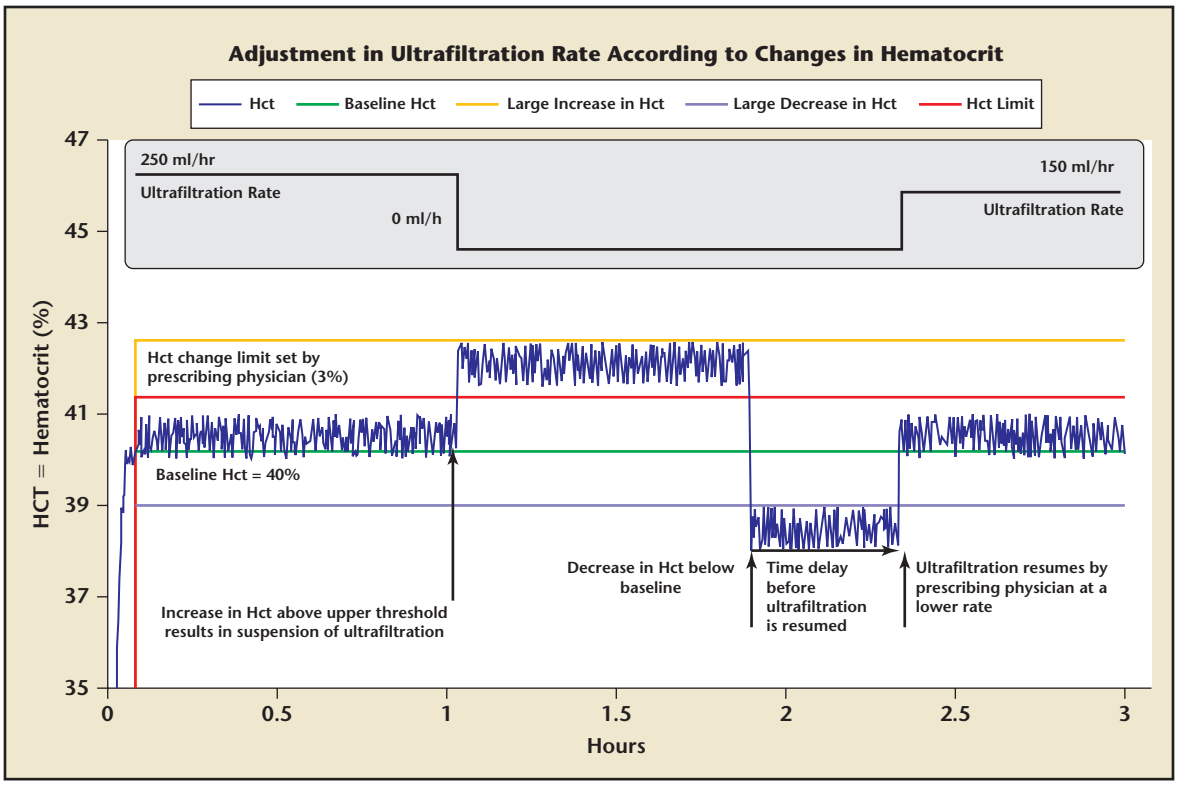


Figure 3. Use of the hematocrit (Hct) sensor to estimate blood volume and adjust fluid removal rates. During ultrafiltration (UF) therapy, blood passes through a small chamber integrated with the withdrawal line. A sensor that uses infrared technology to measure Hct in real time can be clipped to the blood chamber during UF. The first time the Hct sensor is placed on the blood chamber, the device will initiate a 10- to 20-minute process to establish the value of the baseline Hct. Upon completion of this process, the treating physician has the choice of either accepting the default increase in Hct of 5% or establishing a different limit of Hct change as the threshold at which fluid withdrawal is halted. As long as the Hct value measured by the sensor is below the set limit, fluid removal continues at the rate set by the treating physician. In this example, with a UF rate initially set to 250 mL/h the patient's baseline Hct value is determined to be 40%. In this example, the treating physician has set a 3% Hct change (change value) as the limit above which fluid withdrawal will be halted. The change value is used to automatically calculate the upper and lower Hct values (large increase/decrease) and the Hct limit above which UF is suspended (UF rate = 0 mL/h). In this example, where the change value is 3%, the corresponding Hct limit is 41.2% (= 40.0 × 1.03). When the sensor measures an Hct value above 41.2%, fluid withdrawal is halted. When the measured Hct value returns below the set Hct limit, UF will resume either at the rate previously prescribed or, in this case, at a lower rate of 150 mL/h chosen by the treating physician.

or N-terminal-proBNP levels < 4000 pg/mL, especially if associated with clinical evidence of optivolemia, predict favorable outcomes.[44] Although attractive, the approach of targeting fluid removal by UF to achieve these NP levels has not been prospectively evaluated.

Awareness that AKI may occur in ADHF patients as a result of intense decongestion (CRS type 1) has spurred interest in new AKI biomarkers such as neutrophil gelatinase-associated lipocalin and kidney injury molecule.[11] Because the levels of these biomarkers rise before sCr, AKI can be detected earlier and further renal damage due to overly aggressive fluid removal by UF could be prevented.[11]

Bioimpedance Vector Analysis

Bioimpedance vector analysis (BIVA) is based on the principle that whole body impedance to an alternating current, which results from the electrical characteristics of the complex network of resistive and capacitive conductors arranged in parallel and in series within soft tissues, reflects the amount of intra- and extracellular fluid.[45] Measurements can be made in vivo with the application of a 50 kHz alternating microcurrent using a system in which two pairs of electrodes are placed on the wrist and ankles to obtain total body measures (CardioEFG, EFG Diagnostics, Belfast, Northern Ireland). Corrected by height, BIVA measurements of impedance, resistance, reactance, and phase angle are highly correlated with total body water (r = 0.996).[45] Data on age, sex, and height of 1800 white subjects were used to develop nomograms of resistance and reactance that permit us to determine whether a subject is euvolemic, dehydrated, or fluid overloaded.[46] Studies in overhydrated critically ill patients have confirmed the reliability of BIVA to guide volume of fluid removal by UF.[47] It is therefore attractive to envision the utilization of BIVA to determine the fluid status of ADHF patients before initiation of UF and then use serial BIVA measurements to guide the

amount and rate of fluid removal by UF, so that resolution of congestion does not occur at the expense of reductions in renal blood flow and perfusion pressure sufficiently severe to cause AKI (CRS type 1).[48] Although the BIVA system is not yet approved for clinical use in the United States, at several European centers, BIVA has been used during UF in conjunction with estimates of blood volume, because the former estimates the amount of fluid to be removed, whereas the latter can help to adjust the rate of fluid removal.[48]

Accuracy of bioimpedance measures can be reduced by many factors, including diaphoresis, hirsutism, incorrect placement of the electrodes, cutaneous alterations (eg, ulcers, wounds), or improper electrical grounding.

Conclusions

For more than a century, sodium has been recognized as the major determinant of extracellular fluid volume in HF. Therefore, excess total body sodium should be the principal target for the therapy of patients hospitalized for worsening symptoms and signs of congestion. Loop diuretics are inherently incapable of consistently reducing total body sodium. Indeed, despite the nearly universal use of loop diuretics, death and rehospitalization rates for ADHF patients remain unacceptably high. Because of its mechanism, UF predictably reduces total body sodium. However, safe and effective decongestion by UF requires both careful selection of candidates for the therapy and fine-tuning of fluid removal rates according to each patient's hemodynamics and renal function. The disappointing results of the CARRESS-HF trial indicate that failure to tailor fluid removal rates to individual patients' clinical characteristics is unlikely to produce favorable outcomes.

The adverse effects of UF in the CARRESS-HF population versus the sustained benefits observed in the UNLOAD trial suggest that initiation of UF in ADHF patients before they fail high-dose IV diuretics is a strategy that is both safer and more effective.

The questions raised by the results of CARRESS-HF underscore the need to further investigate the role of UF in heart failure patients. The aim of the ongoing Aquapheresis versus Intravenous Diuretics and Hospitalizations for Heart Failure (AVOID-HF) trial (NCT01474200), with more than 800 subjects being enrolled at 40 US centers, is to determine if a strategy of early UF, initiated before worsening of renal function by other therapies, is superior to IV diuretics in reducing 90-day heart-failure–related hospitalizations in ADHF patients. ■

Dr. Costanzo receives consulting and speaking honoraria from Gambro UF Solutions (Minneapolis, MN); Dr. Costanzo's institution receives research funding from Gambro UF Solutions; Dr. Chawla receives consulting and speaking honoraria from Gambro UF Solutions, Nxstage Medical (Lawrence, MA), and Alere (Waltham, MA); Dr. Kellum receives grant support and consulting honoraria from Baxter (Deerfield, IL), Gambro UF Solutions, and Alere; Dr. Ronco receives speaking honoraria from Abbott Laboratories (Abbott Park, IL), Alere, and Gambro UF Solutions; Drs. Herzog, McCullough, and Tumlin have no disclosures.

References

1. Dickstein K, Cohen-Solal A, Filippatos G, et al; ESC Committee for Practice Guidelines (CPG). ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur Heart J.* 2008;29:2388-2442.
2. Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict

MAIN POINTS

- Approximately 70% of patients hospitalized with acute decompensated heart failure (ADHF) have pulmonary and/or venous congestion. Resultant hemodynamic abnormalities contribute to the impairment of kidney function observed in at least 30% of ADHF patients. As a result, it is not surprising that ADHF patients with congestion have a twofold increase in 60-day mortality compared with patients without congestion.
- There are unmet therapeutic needs for a subset of ADHF patients at risk of developing the acute cardiorenal syndrome type 1, which justify the interest in exploring the role of alternative methods of fluid removal, such as isolated venovenous ultrafiltration (UF), in this population.
- The conflicting results on the effects of UF as a method for fluid removal in ADHF patients highlight the importance of patient selection and choice of fluid removal targets. Due to the potential complications and cost of UF therapy, it should not be used indiscriminately in all ADHF patients. The clinical challenge is deciding which patients who develop ADHF despite daily oral diuretic doses should be considered for early UF rather than intravenous diuretics.

outcomes in patients admitted with heart failure. *J Am Coll Cardiol.* 2003;41:1797-1804.
3. Bram B, Cupples WA, Joles JA, Gaillard C. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. *Heart Fail Rev*. 2012;17:161-175.
4. Heywood JT, Fonarow GC, Costanzo MR, et al; ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. *J Card Fail*. 2007;13:422-430.
5. Gheorghiade M, Gattis WA, O'Connor CM, et al; Acute and Chronic Therapeutic Impact of a Vasopressin Antagonist in Congestive Heart Failure (ACTIV in CHF) Investigators. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA*. 2004;291:1963-1971.
6. Schlatter E, Salomonsson M, Persson AE, Greger R. Macula densa cells sense luminal NaCl concentration via furosemide sensitive Na+2Cl-K+ cotransport. *Pflugers Arch*. 1989;414:286-290.
7. Felker GM, Lee KL, Bull DA, et al; NHLBI Heart Failure Clinical Research Network. Diuretic strategies in patients with acute decompensted heart failure. *N Engl J Med*. 2011;364:797-805.
8. Costanzo MR, Jessup M. Treatment of congestion in heart failure with diuretics and extracorporeal therapies: effects on symptoms, renal function, and prognosis. *Heart Fail Rev*. 2012;17:313-324.
9. Ronco C, Ricci Z, Bellomo R, Bedogni F. Extacorporeal ultrafiltration for the treatment of overhydration and congestive heart failure. *Cardiology*. 2001;96: 155-168.
10. Jaski BE, Ha J, Denys BG, et al. Peripherally inserted veno-venous ultrafiltration for rapid treatment of volume overloaded patients. *J Card Fail*. 2003;9:227-231.
11. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52:1527-1539.
12. Kellum JA, Bellomo R, Ronco C. Acute Dialysis Quality Initiative (ADQI): methodology. *Int J Artif Organs*. 2008;31:90-93.
13. Costanzo MR, Saltzberg M, O'Sullivan J, Sobotka P. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J Am Coll Cardiol*. 2005;46:2047-2051.
14. Agostoni P, Marenzi G, Lauri G, et al. Sustained improvement in functional capacity after removal of body fluid with isolated ultrafiltration in chronic cardiac insufficiency: failure of furosemide to provide the same result. *Am J Med*. 1994;96:191-199.
15. Bart BA, Boyle A, Bank AJ, et al. 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. *J Am Coll Cardiol*. 2005;46:2043-2046.
16. Liang KV, Hiniker AR, Wiliams AW, et al. Use of a novel ultrafiltration device as a treatment strategy for diuretic resistant, refractory heart failure: initial clinical experience in a single center. *J Cardiac Fail*. 2006;12:707-714.
17. Rose EA, Gelijins AC, Moskowitz AJ, et al; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345:1435-1443.
18. Cipolla CM, Grazi S, Rimondini A, et al. Changes in circulating norepinephrine with hemofiltration in advanced heart failure. *Am J Cardiol*. 1990;66:987-994.
19. Marenzi G, Grazi S, Giraldi F, et al. Interrelation of humoral factors, hemodynamics, and fluid and salt metabolism in congestive heart failure: effects of extracorporeal ultrafiltration. *Am J Med*. 1993;94:49-56.
20. Costanzo MR, Guglin ME, Saltzberg MT, et al; UNLOAD Trial Investigators. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49:675-683.
21. Elkayam U, Hatamizadeh P, Janmohamed M. The challenge of correcting volume overload in hospitalized patients with decompensated heart failure. *J Am Coll Cardiol*. 2007;49:684-686.
22. Costanzo MR, Saltzberg MT, Jessup M, et al; Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure (UNLOAD) Investigators. Ultrafiltration is associated with fewer re-hospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. *J Card Fail*. 2010;16:277-284.
23. Ali SS, Olinger CC, Sobotka PA, et al. Loop diuretics can cause clinical natriuretic failure: a prescription for volume expansion. *Congest Heart Fail*. 2009;15:1-4.
24. Konstam MA, Gheorghiade M, Burnett JC Jr, et al; Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study With Tolvaptan (EVEREST) Investigators. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297:1319-1331.
25. Abdallah JG, Schreier RW, Edelstein C, et al. Loop diuretic infusion increases thiazide-sensitive Na(+)/Cl(-)-cotransporter abundance: role of aldosterone. *J Am Soc Nephrol*. 2001;12:1335-1341.
26. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol*. 2009;53:589-596.
27. Jessup M, Costanzo MR. The cardiorenal syndrome: do we need a change of strategy or a change of tactics? *J Am Coll Cardiol*. 2009;53:597-599.
28. Ross EA. Congestive heart failure: the pathophysiology and treatment of renal venous hypertension. *J Cardiac Fail*. 2012;18:930-938.
29. Bart BA, Goldsmith SR, Lee KL, et al; Heart Failure Clinical Research Network. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012:367:2296-2304.
30. Bart BA, Goldsmith SR, Lee KL, et al. Cardiorenal rescue study in acute decompensated heart failure: rationale and design of CARRESS-HF, for the Heart Failure Clinical Research Network. *J Cardiac Fail*. 2012;18:176-182.
31. Testani JM, Chen J, McCauley BD, et al. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. *Circulation*. 2010;122:265-272.
32. Bartone C, Saghir S, Menon SG, et al. Comparison of ultrafiltration, nesiritide, and usual care in acute decompensated heart failure. *Congest Heart Fail*. 2008;14:298-301.
33. Patarroyo M, Wehbe E, Hanna M, et al. Cardiorenal outcomes after slow continuous ultrafiltration therapy in refractory patients with advanced decompensated heart failure. *J Am Coll Cardiol*. 2012;60:1906-1912.
34. Dev S, Shirolkar SC, Stevens SR, et al. Reduction in body weight but worsening renal function with late ultrafiltration for treatment of acute decompensated heart failure. *Cardiology*. 2012;123:145-153.
35. Costanzo MR, Ronco C. Isolated ultrafiltration in heart failure patients. *Curr Cardiol Rep*. 2012;14: 254-264.
36. Singh P, Rifkin DE, Blantz RC. Chronic kidney disease: an inherent risk factor for acute kidney injury? *Clin J Am Soc Nephrol*. 2010;5:1690-1695.
37. Tang WH. Reconsidering ultrafiltration in the acute cardiorenal syndrome. *N Engl J Med*. 2012;367: 2351-2352.
38. Jessup M, Abraham WT, Casey DE, et al. 2009 focused update: ACCF/AHA Guidelines for the Diagnosis and Management of Heart Failure in Adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the International Society for Heart and Lung Transplantation. *Circulation*. 2009;119:1977-2016.
39. Gheorghiade M, Follath F, Ponikowski P, et al. Assessing and grading congestion in acute heart failure: a scientific statement from the acute heart failure committee of the heart failure association of the European Society of Cardiology and endorsed by the European Society of Intensive Care Medicine. *Eur J Heart Fail*. 2010;12:423-433.
40. Marenzi G, Lauri G, Grazi M, et al. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. *J Am Coll Cardiol*. 2001;38:963-968.
41. Stawicki SP, Braslow BM, Panebianco NL, et al. Intensivist use of hand-carried ultrasonography to measure IVC collapsibility in estimating intravascular volume status: correlation with CVP. *J Am Coll Surg*. 2009;209:55-61.
42. Ronco C, Brendolan A, Bellomo R. Online monitoring in continuous renal replacement therapies. *Kidney Int*. 1999;56(suppl):S8-S14.
43. Maisel AS, Krishnaswamy P, Nowak RM, et al; Breathing Not Properly Multinational Study Investigators. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Eng J Med*. 2002;347:161-167.
44. Logeart D, Thabut G, Jourdain P, et al. Predischarge B-type natriuretic peptide assay for identifying patients at high risk of re-admission after decompensated heart failure. *J Am Coll Cardiol*. 2004;43:635-641.
45. Piccoli A, Nigelli S, Caberlotto A, et al. Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. *Am J Clin Nutr*. 1995;61:269-270.
46. Piccoli A. Whole body—single frequency bioimpedance. *Contrib Nephrol*. 2005;149:150-161.
47. Ronco C, Kaushik M, Valle R, et al. Diagnosis and management of fluid overload in heart failure and the cardio-renal syndrome: the "5B" approach. *Semin Nephrol*. 2012;32:129-141.
48. Costanzo MR, Cozzolino M, Aspromonte N, et al. Extracorporeal ultrafiltration in heart failure and cardiorenal syndromes. *Semin Nephrol*. 2012;32:100-111.