CHAPTER 119

Management of Overhydration in Heart Failure Patients

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OBJECTIVES

This chapter will:

1. Describe the current treatment options for decongestion in acute decompensated heart failure.
2. Review key clinical trials of ultrafiltration in heart failure management.
3. Describe clinical goals and targets of obtaining adequate decongestion.

It is estimated that more than one million patients are hospitalized annually with the primary diagnosis of acute decompensated heart failure (ADHF).[1] More than 70% of these patients have pulmonary and/or venous congestion when initially seen.[2] Among these fluid-overloaded patients, cardiac output (CO) can be either normal or decreased. Congestion in the setting of preserved CO may result in increased renal venous pressure and impaired renal autoregulation, whereas congestion with reduced CO may be associated with increased renal venous pressure and decreased renal blood flow.[3] These hemodynamic abnormalities lead to the impairment of kidney function seen in at least 30% of ADHF patients.[4] Therefore it is not surprising that ADHF patients with congestion that persists after initial hospital therapy have a twofold increase in 60-day mortality compared with patients without congestion.[5] Loop diuretics, used to decrease congestion in approximately 90% of ADHF patients, have important limitations. The enhanced neurohormonal activation known to occur with the administration of loop diuretics can result in further exacerbation of hemodynamic abnormalities complicating ADHF.[6] Therefore alternative decongestive strategies such as isolated venovenous ultrafiltration (UF) have been used for ADHF patients at risk for the development of acute cardiorenal syndromes (CRS). This chapter reviews the various therapeutic options available for management of congestion in heart failure.

DIURETICS

Loop diuretics are the most commonly used therapy for the treatment of congestion in ADHF. Loop diuretics augment natriuresis and diuresis by inhibiting the Na-K-2Cl cotransporter, expressed in the thick ascending limb of the loop of Henle of the nephron. This cotransporter, however, 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 chloride transport into the macula densa, loop diuretics elicit a heightened secretion of renin.[3,7] Therefore the very mechanism of action of loop diuretics results in stimulation of renin release and upregulation of the detrimental neurohormonal cascade that contributes to the progression of heart failure. Data from the Diuretic Optimization Strategies Evaluation (DOSE) trial show that 42% of ADHF patients reached the composite end point 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.[8] These data underscore the unmet therapeutic needs of ADHF patients, which justifies exploration of alternative methods of fluid removal, such as isolated venovenous UF.[9,10] The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial has shown that, in the setting of acute CRS, careful adjustment in diuretic doses with an aggressive stepped pharmacologic therapy (SPT) algorithm, which also included vasoactive therapy titrated to patients' blood pressure, urine output, and changes in renal function, can result in effective decongestion of ADHF patients with prior worsening renal function (WRF).[11] However, even with aggressive therapies the outcomes of the CARRESS-HF population were poor: more than 30% of patients treated died or were readmitted for ADHF within 60 days of the index hospitalization.[11,12] The diminished overall efficacy of loop diuretics may in part be explained by the underrecognition of their pharmacokinetic profiles, bioavailability, and elimination half-life, which may lead to inadequate dosing levels and frequency of administration. Close attention to appropriate diuretic targets tailored to individual patients can improve the therapeutic effects of loop diuretics. Often, sequential nephron blockade with thiazide-type diuretics and addition of aldosterone antagonists are required to maintain diuretic efficacy for optimal decongestion and reduction of diuretic resistance in the ADHF patient population. Vasopressin antagonists also have been used for free water removal in conjunction with loop diuretics for patients with heart failure and hyponatremia. In the study of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial, vasopressin antagonists produced greater decongestion than IV loop diuretics alone but were not associated with improved mortality or cardiovascular morbidity.[13] Equally disappointing was the adenosine antagonist rolofylline, which did not produce the expected favorable effect on renal function and did not favorably affect long-term outcomes in ADHF.[14,15] Among pharmacologic therapies that did have a positive impact on renal function, the novel vasodilator serelaxin was shown in the Relaxin in Acute Heart Failure Study (RELAX-AHF) to decrease the incidence of WRF, as defined by a rise in serum creatinine (SCr) or cystatin C, as well as to reduce 180-day mortality in ADHF patients.[16] The utility of this recombinant hormone is being investigated further in the Relaxin in Acute Heart Failure Study 2 (RELAX-AHF 2).

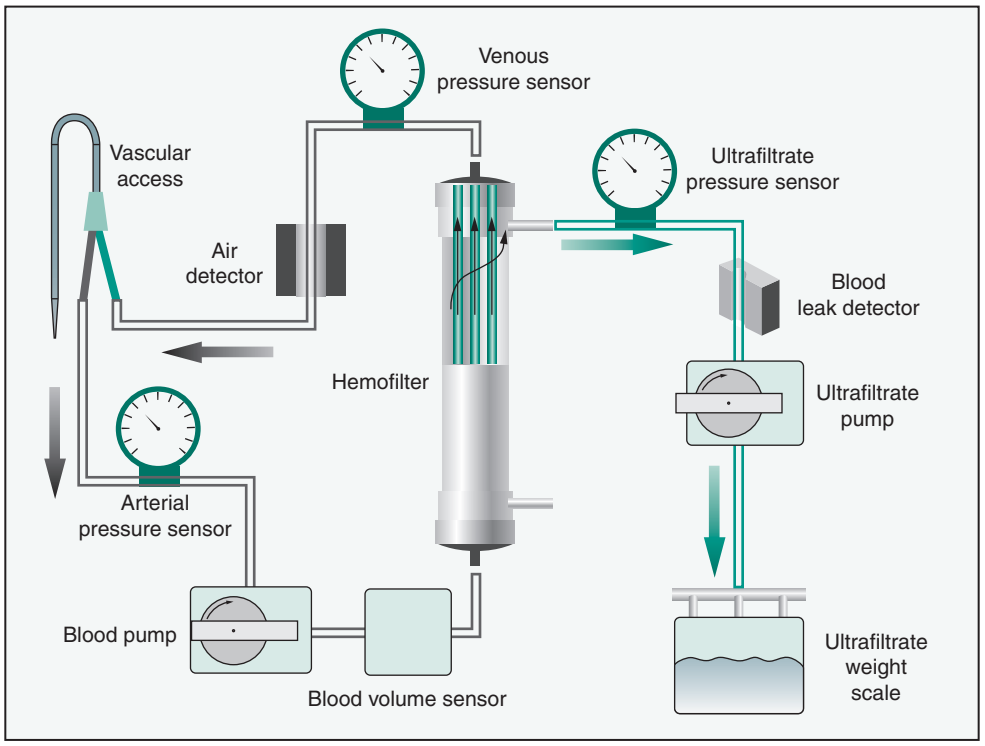

FIGURE 119.1 Isolated venovenous ultrafiltration circuit. Blood is withdrawn through a vein through the withdrawal catheter of the vascular access into the blood pump and onto the hemofilter, where ultrafiltration of isotonic fluid is removed at a controlled rate set by the physician. Blood then is transmitted back to the patient, and the ultrafiltrate is stored in a collecting bag. Reprinted with permission of MedReviews®, LLC. Costanzo MR et al. The role of early and sufficient isolated venovenous ultrafiltration in heart failure patients with pulmonary and systemic congestion.*Rev Cardiovasc Med.* 2013;14(2–4):e123–e133. All rights reserved.

Ultrafiltration

Isolated venovenous UF is a method of decongestion that can be used as an alternative to loop diuretics. UF has been made feasible with the advent of simplified devices that permit volume removal with peripheral venous access, adjustable blood flow, and small extracorporeal blood volumes (Fig. 119.1).[17] With this therapy, plasma water is produced from whole blood across a semipermeable membrane (hemofilter) in response to a transmembrane pressure gradient that is driven by hydrostatic forces generated by extracorporeal pumps. These hydrostatic forces can be adjusted manually, allowing for tightly controlled UF fluid removal rates. The solute concentration in the ultrafiltrate is equal to that in the water component of the plasma, allowing for effective isotonic sodium removal from the patient.[18] 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.[17] This study showed that, in 21 congested 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, SCr, electrolytes, or the occurrence of major adverse events. Several UF studies conducted thereafter were discussed at the 11th Acute Dialysis Quality Initiative (ADQI) meeting and are presented in the following section.[19]

Pilot Studies

One pilot study looked at whether UF begun within 12 hours of admission could restore euvolemia safely, permit discharge in 3 days or less, and prevent 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).[20] Vasoactive drugs and more than one dose of intravenous (IV) loop diuretic were prohibited before initiation of UF. An average of 8654 ± 4205 mL was removed with 2.6 ± 1.2 8-hour UF sessions. Twelve patients (60%) were discharged in 3 days or less. 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.[20] Remarkably, in seven patients with hyponatremia (serum sodium ≤ 135 mg/dL), sodium increased from pretreatment values at discharge ($p = .042$) and at 90 days ($p = .017$). Given that ultrafiltrate is isotonic with plasma, the rise in serum sodium was not attributed to direct effects of UF, but rather to attenuation of neurohormonal activation, as indicated by the decrease in plasma BNP levels without worsening renal function.[21] The results of this pilot study suggested that, in ADHF patients with diuretic resistance, UF initiated *early* before therapy with IV loop diuretics effectively decreased readmissions and length of stay, with clinical benefits extending to 90 days.[20] This preliminary study 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 reflect the fact that fluid removal by UF occurred before upregulation of neurohormonal activity by IV loop diuretics.[21] 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.[22] Weight loss, the primary end point 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.[22] As in the previous study, effective decongestion and clinical improvement were observed with *early* initiation of UF, before elevation of SCr levels resulting from IV loop diuretic dosing.[9,20–22] Again, study limitations must be recognized, given the small sample size and lack of assessment of outcomes beyond 48 hours.[22] A single-center study of 11 patients with advanced diuretic resistant heart failure (defined by pretreatment average SCr of 2.2 mg/dL, mean estimated glomerular filtration rate [eGFR] of 38 mL/min [with 6/11 having eGFR < 30 mL/min]), mean daily IV furosemide dose of 258 mg, including nine patients [82%] with documented severe right ventricular [RV] dysfunction, and three patients [27%] with pericardial constriction) provides valuable insight on the appropriate use of UF in ADHF patients.[23] This study sought to remove a goal of 4 L of fluid with each 8-hour UF course, which was achieved in only 13 of 32 treatments (41%). Five patients (45%) experienced an increase in SCr of more than 0.3 mg/dL, and five patients required hemodialysis (HD). There was no obvious correlation between amounts of fluid removed by UF and the need for HD.[23] The severity of illness of these patients is exemplified by the 55% 6-month mortality noted in this trial. Such mortality rate was 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 heart failure clinical trial.[24]

Based on these observations, one can deduce several key points in the use of UF therapies: (1) isolated venovenous UF does not significantly alter the outcomes of patients with end-stage heart failure, and (2) fast fluid removal rates should be used with caution because they can be very detrimental to cardiorenal physiology, particularly in patients with RV dysfunction who are exquisitely susceptible to intravascular hypovolemia because of the storage of a larger proportion of blood in the venous circulation. Thus rapid removal of volume with aggressive UF in heart failure patients with RV dysfunction can decrease renal perfusion pressure, cause a rise in SCr, and convert nonoliguric renal dysfunction into oliguric failure and subsequent dialysis dependence.[23,25,26] High doses of IV loop diuretics before UF, by intensifying neurohormonal activation, may predispose the kidney to injury by additional fluid removal with UF.

Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Heart Failure Trial

The goal 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.[27] A total of 200 patients (aged 63 ± 15 years; 69% men; 71% ejection fraction ≤ 40%) were randomized to UF or IV diuretics. At 48 hours, weight (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; $p = .001$) and net fluid loss (4.6 L vs. 3.3 L; $p = .001$) were greater in the UF group.[27] Dyspnea was improved similarly in the two groups. At 90 days, the UF group had fewer patients rehospitalized for heart failure (18% vs. 32%; $p = .037$) and fewer unscheduled visits for worsening heart failure (21% vs. 44%; $p = .009$). A similar percentage of patients with increases in SCr levels exceeding 0.3 mg/dL was noted 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.[27] Occurrences of hypokalemia (serum potassium < 3.5 mEq/L) were fewer in the UF than in the diuretic group (1% vs. 12%; $p = .018$), and episodes of hypotension during treatment were rare in both groups (4% vs. 3%).[27] Complications 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.[27]

The UNLOAD trial lacked treatment targets, blood volume assessments, and cost analysis. However, the salient findings of this trial still provide valuable lessons: 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. A posthoc analysis from the UNLOAD trial reviewed the outcomes of 100 patients treated with UF 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).[28] 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 ($p = .016$).[28] Volume overload in heart failure (HF) patients occur in relation to an increase and abnormal distribution of total body sodium.[29] The greater reduction of total body sodium by isotonic fluid removal may be more effective than elimination of hypotonic fluid by diuretics or isolated free water by vasopressin V_2 receptor blockers.[13,29] It is also possible that prehospitalization diuretic use reduces the natriuresis achievable with the subsequent administration of IV loop diuretics.[30] Increased central venous pressure (CVP) is associated independently with worsening renal function.[31] The increased amounts of sodium and water reabsorbed by the kidney because of neurohormonal upregulation predominantly fill the compliant venous circulation, increasing CVP. Transmission of venous congestion to the renal veins further impairs GFR.[21,32,33] Successful lowering of CVP without development of WRF calls for effective use of UF with establishment of fluid removal rates that do not exceed capillary refill rates, so adequate intravascular volume is maintained.[10] This raises the concept of the plasma refill rate (PRR) (mL/min), which is a measurement of the fluid volume transport from the interstitium into the vascular space during UF, expressed as filtrate volume/time, where time is the duration of UF.[18] Fluid removal rates can be titrated to be equal or lower than the PRR so that refilling of the intravascular space by the excess fluid in the interstitial space is maintained, and the likelihood of worsening intravascular volume depletion is reduced. Maintenance of an adequate blood volume reduces the risk of the development of WRF during decongestion of ADHF patients.[32,33]

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/hr, with those of 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.[11] All subjects therefore were in the midst of CRS type 1 with an acute rise in SCr at the time of randomization. The primary end point was the bivariate change from baseline in SCr level and body weight, as assessed 96 hours after randomization.[34] In the patient population of CARRESS-HF, UF was inferior to SPT with respect to the 96-hour bivariate end point, 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.[11]

The results and design of CARRESS-HF deserve further scrutiny. The simultaneous consideration of changes in SCr and weight may have been misleading. 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 [HCT], albumin, or total protein) after decongestive therapy was associated strongly with worsening renal function, defined as at least a 20% decrease in eGFR. However, despite a higher incidence of this change in renal function from diuresis, patients with hemoconcentration had a significantly lower 180-day mortality (hazard ratio, 0.31; $p = .013$).[35] Thus aggressive decongestion of ADHF patients does not necessarily worsen outcomes. Interestingly, a retrospective review of 845 patients discharged from a single center with a primary diagnosis of heart failure showed that hemoconcentration occurring *late* (time of the peak HCT level occurring at >50% of length of index hospital stay) after treatment of ADHF predicted improved survival (HR: 0.74, 95% CI: 0.59 to 0.93; $p = .009$), whereas *early* hemoconcentration did not, despite similar WRF in both groups.[36]

Late hemoconcentration may reflect hemodynamic mediated changes in SCr in response to appropriate decongestive strategies, whereas early hemoconcentration may indicate the presence of intrinsic kidney injury or therapy-induced excess intravascular volume depletion.[37] In a retrospective comparison of 25 patients with UF, 25 patients with IV diuretics, and 25 patients treated with nesiritide, 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 these 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).[38] 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 an 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.[8] Thus transient increases in SCr resulting from decongestive therapies are not always predictive of adverse long-term outcomes, because they may be indicative only of temporary hemoconcentration. The rate of fluid removal in CARRESS-HF was mandated to be the same (200 mL/hr) in all patients assigned to the UF arm, and no adjustments were allowed according to patients' vital signs, 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.[11] However, a UF rate of 200 mL/hr may have exceeded the PRR for patients with lower blood pressure and/or RV dysfunction and may have resulted in worsening renal function because of relative arterial intravascular volume depletion.

Although the incidence and severity of RV dysfunction was not reported in the CARRESS-HF study, it is important to understand that these patients are at a greater risk of intravascular depletion from fluid removal because of an increased proportion of blood volume being stored in the venous circulation.[23,39,40] Clinical experience shows that, regardless of the method used for decongestion, removal of fluid must be individualized, with careful consideration of patients' blood pressure, renal function, body mass, and urine output. Review of the design manuscript of the CARRESS trial reveals that in the SPT group a careful treatment algorithm allowed 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.[34] This dynamic flexibility in pharmacologic therapy was not paralleled in the UF group. 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.[11] In these patients, the use of positive inotropic agents may have prevented worsening renal function. In addition, a 20% crossover rate was noted in the study; 36 patients (39%) in the UF group 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 primary end point assessment.[11] Based on the high percentage of UF patients who 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 severity and duration of underlying renal dysfunction are key risk factors for the development of AKI.[41] Thus CARRESS-HF was not a prevention trial, such as UNLOAD, but a treatment trial of CRS type 1, in which UF was initiated late after the development of WRF. 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.[11,12]

Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure

The Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial sought to answer the question whether an early strategy of adjustable ultrafiltration (AUF) in patients with ADHF truly was associated with fewer heart failure events at 90 days compared with a strategy based on adjustable intravenous loop diuretics (ALD). The key difference between the clinical trial design of CARRESS-HF and AVOID-HF was that in the latter, regardless of decongestive therapy, fluid removal was individualized according to patients' vital signs, hemodynamic status, and baseline renal function in UF and loop diuretic groups. Fluid removal rates also were titrated during the study to maintain capillary refill rate and avoid intravascular depletion.[42] The diuretic arm of AVOID-HF was similar to that of CARRESS-HF, with the use of an aggressive adjustable pharmacologic protocol (Table 119.1). However, in contrast to CARRESS-HF, adjustable fluid removal rates for UF also were recommended based on a prespecified protocol. Initial UF rates were based on patients' starting blood pressure, with physician discretion for lower initial rates in patients with RV dysfunction or significant baseline renal insufficiency. Adjustments to UF rates during therapy were made based on changes in SCR, urine output, and blood pressure, with the goal of slowly decreasing UF fluid removal rates over the course of decongestion to match the concomitant decline in PRR, thereby effectively allowing extracellular volume to refill the intravascular space at the same rate as volume removal (Box 119.1). This protocol differed from CARRESS-HF recommendations and allowed avoidance of intravascular volume depletion during therapy.[43] UF fluid removal was deemed complete once clinical decongestion was achieved and UF rates were less than 50 mL/hr. Unfortunately, the trial was terminated unilaterally and prematurely by the sponsor (Baxter Healthcare, Deerfield, Illinois) after enrollment of 224 patients (27.5%).

A Clinical Events Committee, blinded to the randomized treatment, adjudicated whether 90-day events were related to HF.[44] A total of 110 patients were randomized to AUF and 114 to ALD. The primary end point of time to first HF event was longer in the AUF group compared with the ALD group (62 days vs. 34 days, $p = .106$), but this difference was not statistically significant, owing to the smaller than originally planned sample size (Fig. 119.2). An HF event within 90 days occurred in 25% of AUF patients and 35% of ALD patients. The hazard ratio of 0.663 (95% confidence interval [CI]: 0.402 to 1.092), which suggests a 37% reduction in the risk of a HF event with AUF versus ALD therapy, was also not statistically significant.[44] Despite the fact that the study was stopped early after the enrollment of only 27.5% of

TABLE 119.1

Treatment Guidelines for the Loop Diuretic Arm in the AVOID Trial

At Randomization
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3–5 L/day → Continue current diuretic regimen
UO < 3 L/day → See table

	CURRENT DOSE			SUGGESTED DOSE
	Loop (/day)	thiazide	Loop (/day)	thiazide
A	≤80	+ or –	40 mg IV bolus +5 mg/hr	0
B	81-160	+ or –	80 mg IV bolus + 10 mg/hr	5 mg metolazone QD
C	161-240	+ or –	80 mg IV bolus + 20 mg/hr	5 mg metolazone BID
D	>240	+ or –	80 mg bolus + 30 mg/hr	5 mg metolazone BID

"Loop" refers to IV furosemide. 1 mg bumetanide or 10 mg torsemide = 40 mg furosemide

At 24 Hours
Persistent volume overload present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3–5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table

At 48 Hours
Persistent volume overload present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3–5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
IV inotropes if SBP < 110 mm Hg and EF < 40% or RV systolic dysfunction.
Nitroglycerin or nesiritide if SBP > 120 mm Hg (any EF) and severe symptoms

At 72 Hours
Persistent volume overload present
UO > 5 L/day → Reduce current diuretic regimen *if desired*
UO 3–5 L/day → Continue current diuretic regimen
UO < 3 L/day → Advance to next step on table and consider:
IV inotropes if SBP < 110 mm Hg and EF < 40% or RV systolic dysfunction
Nitroglycerin or nesiritide if SBP > 120 mm Hg (any EF) and severe symptoms
Right heart catheterization

IV, Intravenous; *LOOP,* loop diuretic; *UO,* UOP. From Costanzo MR, et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF), TABLE III. *Am Heart J.* 2015;170(3):471–482. doi:10.1016/j.ahj.2015.05.019.

BOX 119.1

Treatment Guidelines for the Aquapheresis Arm in the AVOID Trial

General Comments

1. Once an initial UF rate is chosen, avoid increasing the UF rate unless there are clear indications to do so.
2. Because patients' plasma refill rate usually declines as fluid is removed, it should be expected that UF rate will have to be decreased during the course of therapy.
   - A. Choose initial UF rate
     SBP <100 mm Hg: 150 mL/hr
     SBP 100–120 mm Hg: 200 mL/hr
     SBP >120 mm Hg: 250 mL/hr
   - B. Decrease starting UF rate by 50 mL/hr if any of the following are present:
     - a. RV > LV systolic dysfunction
     - b. SCr increase 0.3 mg/dL above recent baseline
     - c. Baseline SCr > 2.0 mg/dL
     - d. History of instability with diuresis or UF in the past
   - C. Re-evaluate UF rate every 6 hours:
     - a. Evaluate recent BP, HR, UO, net intake/output, SCr
     - b. Consider decreasing Aq. by 50 mL/hr and checking STAT SCr (unless sent in past 2 hours) if:
       - I. SCr rise >15% or >0.2 mg/dL (whichever is less) compared with prior measurement
       - II. Resting SBP decreases > 10 mm Hg compared with prior 6 hours, but remains > 80 mm Hg
       - III. UO drops > 50% compared with prior 6 hours, but remains >125 mL/6 hr
       - IV. Resting HR increases by >20 bpm compared with prior 6 hours, but remains <120 bpm
     - c. Strongly consider holding UF and checking STAT SCr if:
       - I. SCr rise by >30% or >0.4 mg/dL (whichever is less) compared with prior measurement
       - II. Resting SBP decreases > 20 mm Hg compared with prior 6 hours or is < 80 mm Hg
       - III. UO < 125 mL/6 hr
       - IV. Resting HR increases by 30 bpm compared with prior 6 hours or is >120 bpm
     - d. If UF held, reevaluate after laboratory values are available:
       - I. If hemodynamics are stable and SCr has plateaued, then consider restarting UF at rate 50–100 mL/hr less than previous rate
       - II. If persistent volume overload is present, then consider:
         - i. IV inotropes in patients with LVEF < 40% or RV systolic dysfunction
         - ii. Weaning venodilators, especially in patients with HFpEF
         - iii. Right heart catheterization
   - D. Consider completion of UF therapy If ONE of the following occurs:
     - a. Resolution of congestion (all of following):
       - I. Jugular venous pressure <8 cm H_2O
       - II. No orthopnea
       - III. Trace or no peripheral edema
     - b. Best achievable "dry weight" has been reached
       - I. Evidence of poor tolerance of fluid removal AND
       - II. UF rate <100 mL/hr or net negative <1 L/24 hr

BP, Blood pressure; *HR,* heart rate; *LV,* left ventricle; *RV,* right ventricle; *SBP,* systolic blood pressure; *SCr,* serum creatinine; *UF,* ultrafiltration; *UO,* urine output. From Costanzo MR, et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF), TABLE IV. *Am Heart J.* 2015;170(3):471–482. doi:10.1016/j.ahj.2015.05.019.

the original sample size, there was still sufficient evidence to show that within 30 days after discharge, compared with the ALD group, patients in the AUF group had, per days at risk, fewer patients rehospitalized for HF (9.5% vs. 20.4%, p =.034), fewer days in the hospital resulting from HF readmissions (68 vs. 172 days, p = .029), lower rehospitalization rates because of a CV event (p = .037), fewer rehospitalization days resulting from a CV event (p = .018), and fewer patients rehospitalized for a CV event (p = .042).[44]

These findings of reduced readmissions for HF mirror UNLOAD trial results, again suggesting that early initiation of UF is the best decongestive strategy for ADHF patients. Greater reduction in total body sodium, decreased renin activation, and restoration of diuretic responsiveness during the index hospitalization may have contributed to the extended duration of benefit with UF compared with loop diuretics.[26] Renal function changes were also similar between groups, confirming the hypothesis that early initiation of UF with adjustable rates (average UF rates were 138 mL/hr) can avoid exceeding the PRR and be an effective decongestive method not associated with greater WRF compared with standard therapy. The longer duration of therapy in AVOID-HF versus that of CARRESS-HF (70 hours vs. 41 hours) also aided in maintaining the stability of renal function noted with UF, despite a larger net fluid loss in the AUF than in the ALD group.[44] The 90-day mortality rate was similar in both arms. More patients experienced an adverse event of special interest or a serious product-related side effect in the AUF than in the ALD group.[44] Because of the trial's early closure, additional trials must address the questions left unanswered by the premature and unilateral termination of the study by the sponsor. The Continuous Ultrafiltration for Congestive Heart Failure Trial (CUORE) adds further credence to data confirming the long-term benefits of UF over diuretics. A total of 56 ADHF patients were randomized to early UF strategy versus standard care, and the same initial treatment strategy was repeated if fluid overload recurred up to 1 year after the index ADHF event. Although the fluid volume removed initially was similar in the two treatment arms, the continued UF strategy led to a reduction in 12-month rehospitalization rates (11% [UF] vs. 48% [diuretics], HR: 0.14, 95% CI: 0.04–0.48; p =.002).[45] The UF group had stable SCr at 6 months and 1 year, whereas the standard care group had rising SCr and need for increasing loop diuretic doses during the same period of time.[45]

Selection of Candidates for Ultrafiltration

The conflicting results of clinical trial data on the effects of UF as a method for fluid removal in ADHF patients emphasize the importance of patient selection. Current guidelines suggest that an inadequate response to an initial dose of IV loop diuretic be treated with an increased dose of the same drug.[2,46] If this measure is not effective, invasive hemodynamic assessment is recommended. Persistent congestion then can 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, then mechanical fluid removal can be considered.[46] These recommendations are in stark contrast to clinical trial data on the efficacy of early intervention with UF therapies and are alarmingly similar to the enrollment criteria required for patient entry in the CARRESS-HF trial. However, the unfavorable outcomes in this patient population, which are distinctly different from the sustained benefits observed in

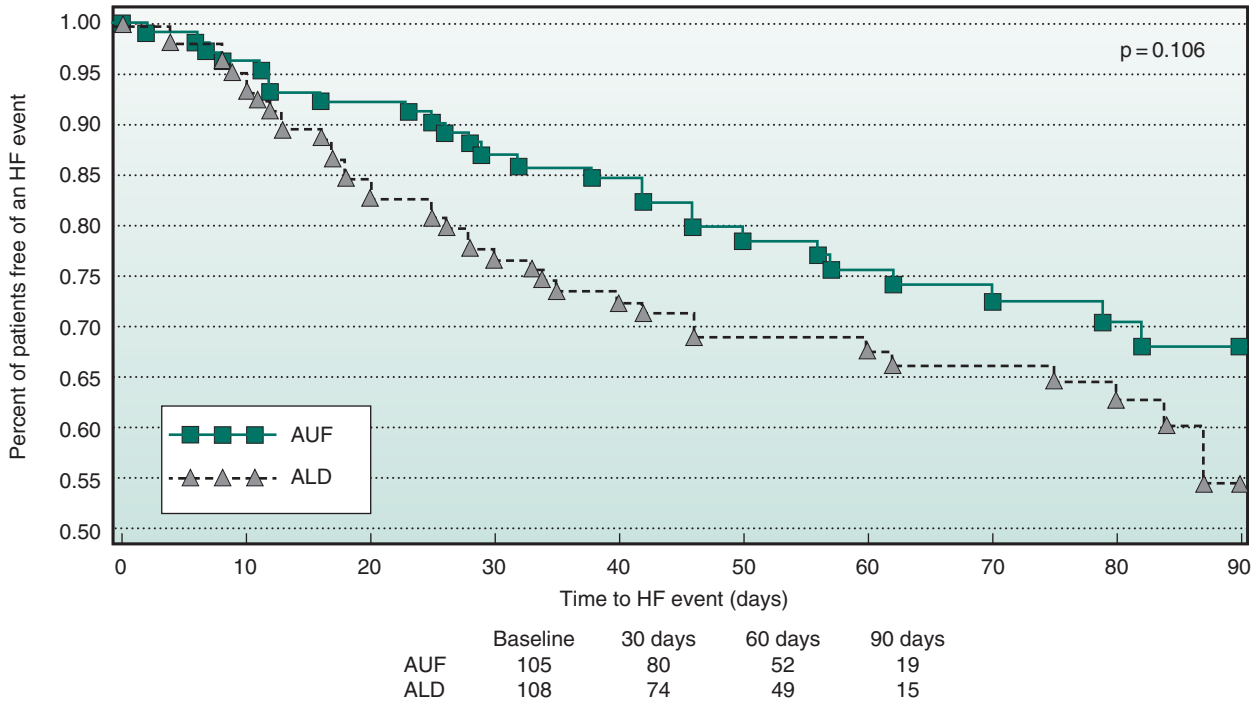

FIGURE 119.2 Primary end point of AVOID-HF trial. A nonstatistical trend toward reduction in time to first heart failure event in the adjustable ultrafiltration (AUF) arm versus the adjustable loop diuretic (ALD) arm (62 days vs. 34 days, $p = .106$), owing to a smaller than originally planned sample size. *HF,* Heart failure. (Reproduced from Costanzo MR, et al. Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure. *JACC Heart Failure.* 2016;4[2]:95–105. doi:10.1016/j.jchf.2015.08.005.)

the UNLOAD and AVOID trial, suggest that initiation of UF in ADHF patients before they fail high-dose IV diuretics is a strategy that is safer and more effective.[a] Because of 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 eliminated rapidly with IV diuretics; therefore these drugs should be used instead of or before UF is considered. The more difficult 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 treated subsequently with UF resulting from 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; $p = .000025$).[29] These results show that urinary sodium concentration in response to IV loop diuretics is lower than the sodium concentration in the ultrafiltrate, as well as highly variable between patients. In the same study no correlation was found between urinary sodium concentration and baseline renal function, which emphasizes the difficulty in predicting the natriuretic response of diuretics in any one individual patient. A recent consensus statement proposes that congestion be graded according to a combination of clinical and laboratory parameters (Table 119.2). The expert consensus suggested that a congestion grade of more than 12 together with low urine output (<1000 mL/24 hr) 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.[47] This recommendation should also be validated prospectively.

Fluid Removal Targets

The safety and efficacy of decongestive strategies depend largely 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 established clearly. Initial UF fluid removal rates are prescribed based upon patients' vital signs and hemodynamic status. Given the fact that PRR continues to decline as decongestion nears closer to euvolemic targets, goal UF rates also are recommended to be reduced slowly from their highest initial starting point to effectively match refilling of the intravascular space. 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 removal. Rates of UF exceeding 250 mL/hr are no longer recommended in patients with ADHF. Patients with predominantly right-sided heart failure or patients with heart failure and preserved systolic function with restrictive physiology can be very susceptible to intravascular volume depletion and may only tolerate UF rates below 150 mL/hr.[18] Extracorporeal fluid removal appears to be better tolerated when conducted with low UF rates over prolonged periods of time (more than 8 hours and up to 72 hours). Unfortunately, in most studies conducted thus far, UF has been used only for short periods of time (≤ 40 hours). Thus the benefits of UF initiated before the onset of the CRS type 1 and performed with low fluid removal

[a]References 11, 20, 22, 23, 27, 40, 44.

TABLE 119.2

Grading Congestion

VARIABLE	SCORE				
	–1	0	1	2	3
Bedside assessment					
Orthopnea[a]		None	Mild	Moderate	Severe/worst
JVP (cm)	<8 and no hepatojugular reflux		8–10 or hepatojugular reflux	11–15	>16
Hepatomegaly	Absent in the setting of normal JVP	Absent	Liver edge	Moderate pulsatile enlargement	Massive tender enlargement extending to midline
Edema		None	1+	2+	3+/4+
Laboratory					
Natriuretic peptides (one)					
BNP		<100	100–299	300–500	>500
NT pro-BNP		<400	400–1500	1500–3000	>3000
Dynamic maneuvers					
Orthostatic testing	Significant decrease in SBP or increase in HR	No change in SBP or HR			
		No difficulty	Mild	Moderate	Severe/worst
6-min walk test	>400 m	300–400 m	200–300 m	100–200 m	<100 m
Valsalva maneuver	Normal response		Absent overshoot pattern	Square wave pattern	

[a]Congestion grade: <1, none; 1–7, mild; 8–14. moderate; 15–20, severe. Edema, in the absence of other cause of edema.
a Orthopnea: 0. absent; mild (use of one pillow); moderate (use of more than one pillow); severe, sleeps in an armchair on in a seated position.
BNP, Brain natriuretic peptide; *HR,* heart rate; *JVP,* jugular venous pressure; *SBP*, systolic blood pressure. Reproduced with permission from Gheorghiade M, 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 Failure.* 2010;12(5):423–433. doi:10.1093/eurjhf/hfq045.

rates for more than 40 hours deserve 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 (perceived dry weight) and remove at least 60% to 80% of this excess fluid without causing hemodynamic instability or worsening renal function.[43] It is reasonable to define resolution of congestion as a jugular venous pressure of less than 8 cm, absence of pulmonary rales, and trace or no edema.[18] Clear 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 renin-angiotensin-aldosterone system (RAAS), and increased inflammation.[3,32,33] 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.[48] Larger prospective, controlled clinical trials are needed to definitively establish if fluid removal goals by UF may best be directed toward CVP rather than other clinical or hemodynamic variables. As an alternate to invasive measures of CVP, ultrasonography can provide estimates of cardiac filling pressures, particularly with the assessment of respiratory excursions of the diameter of the inferior vena cava (IVC). One study of intensive care unit patients undergoing continuous invasive monitoring showed a moderate correlation (r = –0.31) of the IVC collapsibility index with CVP.[49] Although ultrasonography is noninvasive and inexpensive, its reliability depends greatly on the operator's skill and the patient's respiratory effort.[49]

Blood Volume Estimation

Estimates of blood volume remain difficult in the management of decongestive strategies. HCT levels tend to rise when plasma blood volume is decreased effectively. Theoretically, if UF fluid removal rates maintain within the PRR, there should not be a difference between pre- and posttreatment HCT values. Several online HCT sensors (CritLine, 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 to stop fluid removal if the increase in HCT exceeds the threshold set by the treating physician (3%–7%) and resumed when the HCT value falls below the prespecified limit, indicating adequate refilling of the intravascular volume from the interstitial space.[50] However, because numerous factors (including change in body position) can alter HCT values significantly, clinical and laboratory assessments absolutely must be considered to determine the amount of fluid that should be removed. Another method of assessing volume status is nuclear blood pool analysis. This technique uses radioisotopes tagged to red cells or albumin to directly measure blood volume. It correlates well with invasive measurements of cardiac filling pressures in patients presenting with decompensated HF.[51] However, clearly more prospective clinical trials are needed before this diagnostic utility is accepted widely in practice.[52]

Bioimpedance Vector Analysis

As another method of assessing congestion, bioimpedance vector analysis (BIVA) has been used to correlate to total

body water. BIVA is a noninvasive technique that uses the principle that whole body impedance to an alternating current, with a measureable resistance, reflects the amount of intra- and extracellular fluid.[53] Measurements are made with the application of an alternating microcurrent with two pairs of electrodes placed on the wrist and ankles to obtain total body impedance 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).[53] Validated nomograms of resistance and reactance can help to determine whether a subject is euvolemic, dehydrated, or fluid overloaded.[54]

Studies in overhydrated critically ill patients have confirmed the reliability of BIVA to guide volume of fluid removal.[55] Overhydration can result in myocardial stretch and decompensation, whereas dehydration or relative reduction of circulating blood volume can result in distal organ damage resulting from inadequate perfusion. An optimal approach to the management of ideal volume status may be served best by a multifaceted evaluation, incorporating body weight, blood pressure, biomarkers, bioimpedance vector analysis, and blood volume.[56] Serial BIVA measurements may help guide the amount and rate of fluid removal by UF as well, which may minimize the risk of decreased renal blood flow and perfusion pressure sufficiently severe to cause AKI (CRS type 1).[57] 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, with the former estimating the amount of fluid to be removed, and the latter helping to adjust the rate of fluid removal.[57] Accuracy of bioimpedance measures can be reduced by many factors, including diaphoresis, hirsutism, incorrect placement of the electrodes, cutaneous alterations (e.g., ulcers, wounds), or improper electrical grounding. Further clinical trials are warranted to assess the utility of this noninvasive diagnostic tool.

Biomarkers

Natriuretic peptides (NPs) have become important tools in the diagnosis, treatment, and prognostic assessment of patients with heart failure.[58–60] Studies in ADHF patients have shown that predischarge BNP levels, 350 to 400 pg/mL or N-terminal-proBNP levels less than 4000 pg/mL, especially if associated with clinical evidence of optimal volume status, predict favorable outcomes.[61] 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.[19] The levels of these biomarkers have an earlier rise before SCr, and AKI can be detected earlier to prevent further renal damage resulting from overly aggressive fluid removal.[62]

CONCLUSION

Sodium continues to be recognized as the primary contributing factor of extracellular fluid volume in HF. Therefore excess total body sodium should be the principal target for the therapy of patients hospitalized for ADHF. Loop diuretics are inherently inconsistent in reducing total body sodium. This is manifest by the fact that despite nearly universal use of loop diuretics, death and rehospitalization rates for ADHF patients remain unacceptably high. With isotonic fluid removal during UF, predictable reduction of total body sodium can occur. However, careful selection of candidates for UF and careful adjustment of fluid removal rates are required to maintain safety and efficacy of this therapy. The disappointing results of the CARRESS-HF trial speak to the failure of titrating fluid removal rates to individual patients' clinical characteristics. The questions raised by the results of CARRESS-HF underscore the need to further investigate the role of early intervention with UF in ADHF, before patients fail diuretic therapies and develop WRF. Despite early termination of the study, the AVOID trial still had sufficient evidence to show a reduction in HF readmissions with the use of UF, favoring early intervention strategies as well as the utility of adjustable fluid removal rates to avoid intravascular depletion and WRF. Strategies to better identify total body water and blood volume assessment also must be further studied and validated to better restore patients safely to normovolemia. Future biomarkers of AKI may help prevent renal deterioration with decongestion strategies.

Key Points

1. Removal of excess total body sodium remains the principal target for the therapy of patients hospitalized for acute decompensated heart failure.
2. Loop diuretics are inherently inconsistent in reducing total body sodium.
3. Ultrafiltration provides isotonic fluid removal with predictable reduction of total body sodium.
4. Conflicting results from clinical trials involving ultrafiltration involve variation in patient selection, timing of initiation, and rates of volume removal.
5. Strategies to better identify total body water and blood volume assessment need further study and validation and may help prevent renal deterioration with decongestion strategies.

Key References

18. Costanzo MR, Ronco C. Isolated ultrafiltration in heart failure patients. *Curr Cardiol Rep.* 2012;14(3):254-264. doi:10.1007/s11886-012-0257-y.
35. 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(3):265-272. doi:10.1161/circulationaha.109.933275.
36. Testani JM, Brisco MA, Chen J, et al. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol.* 2013;62(6):516-524. doi:10.1016/j.jacc.2013.05.027.
43. Costanzo MR, Chawla LS, Tumlin JA, et al. The role of early and sufficient isolated venovenous ultrafiltration in heart failure patients with pulmonary and systemic congestion. *Rev Cardiovasc Med.* 2013;14(2-4):e123-e133.
44. Costanzo MR, Negoianu D, Jaski BE, et al. Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure. *JACC Heart Fail.* 2016;4(2):95-105. doi:10.1016/j.jchf.2015.08.005.

A complete reference list can be found online at ExpertConsult.com.

References

1. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics–2014 update: a report from the American Heart Association. *Circulation*. 2014;129(3):e28-e292. doi:10.1161/01.cir.0000441139.02102.80.
2. Dickstein K, Cohen-Solal A, Filippatos G, et al. 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 J Heart Fail*. 2008;10(10):933-989. doi:10.1016/j.ejheart.2008.08.005.
3. Braam B, Cupples WA, Joles JA, et al. Systemic arterial and venous determinants of renal hemodynamics in congestive heart failure. *Heart Fail Rev*. 2012;17(2):161-175. doi:10.1007/s10741-011-9246-2.
4. Heywood JT, Fonarow GC, Costanzo MR, et al. 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(6):422-430. doi:10.1016/j.cardfail.2007.03.011.
5. Gheorghiade M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA*. 2004;291(16):1963-1971. doi:10.1001/jama.291.16.1963.
6. Giglioli C, Landi D, Cecchi E, et al. Effects of ULTRAfiltration vs. DIureticS on clinical, biohumoral and haemodynamic variables in patients with deCOmpensated heart failure: the ULTRADISCO study. *Eur J Heart Fail*. 2011;13(3):337-346. doi:10.1093/eurjhf/hfq207.
7. Schlatter E, Salomonsson M, Persson AE, et al. Macula densa cells sense luminal NaCl concentration via furosemide sensitive Na+2Cl-K+ cotransport. *Pflugers Arch*. 1989;414(3):286-290.
8. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med*. 2011;364(9):797-805. doi:10.1056/NEJMoa1005419.
9. 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(2):313-324. doi:10.1007/s10741-011-9248-0.
10. Ronco C, Ricci Z, Bellomo R, et al. Extracorporeal ultrafiltration for the treatment of overhydration and congestive heart failure. *Cardiology*. 2001;96(3-4):155-168.
11. Bart BA, Goldsmith SR, Lee KL, et al. Ultrafiltration in decompensated heart failure with cardiorenal syndrome. *N Engl J Med*. 2012;367(24):2296-2304. doi:10.1056/NEJMoa1210357.
12. Tang WH. Reconsidering ultrafiltration in the acute cardiorenal syndrome. *N Engl J Med*. 2012;367(24):2351-2352. doi:10.1056/NEJMe1212881.
13. Konstam MA, Gheorghiade M, Burnett JC Jr, et al. Effects of oral tolvaptan in patients hospitalized for worsening heart failure: the EVEREST Outcome Trial. *JAMA*. 2007;297(12):1319-1331. doi:10.1001/jama.297.12.1319.
14. Massie BM, O'Connor CM, Metra M, et al. Rolofylline, an Adenosine A1–Receptor Antagonist, in Acute Heart Failure. *NEJM*. 2010;363(15):1419-1428, doi:10.1056/NEJMoa0912613.
15. Cotter G, Dittrich HC, Weatherley BD, et al. The PROTECT pilot study: a randomized, placebo-controlled, dose-finding study of the adenosine A1 receptor antagonist rolofylline in patients with acute heart failure and renal impairment. *J Card Fail*. 2008;14(8):631-640. doi:10.1016/j.cardfail.2008.08.010.
16. Metra M, Cotter G, Davison BA, et al. Effect of serelaxin on cardiac, renal, and hepatic biomarkers in the Relaxin in Acute Heart Failure (RELAX-AHF) development program: correlation with outcomes. *J Am Coll Cardiol*. 2013;61(2):196-206. doi:10.1016/j.jacc.2012.11.005.
17. 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(3):227-231. doi:10.1054/jcaf.2003.28.
18. Costanzo MR, Ronco C. Isolated ultrafiltration in heart failure patients. *Curr Cardiol Rep*. 2012;14(3):254-264. doi:10.1007/s11886-012-0257-y.
19. Ronco C, Haapio M, House AA, et al. Cardiorenal syndrome. *J Am Coll Cardiol*. 2008;52(19):1527-1539. doi:10.1016/j.jacc.2008.07.051.
20. Costanzo MR, Saltzberg M, O'Sullivan J, et al. Early ultrafiltration in patients with decompensated heart failure and diuretic resistance. *J Am Coll Cardiol*. 2005;46(11):2047-2051. doi:10.1016/j.jacc.2005.05.099.
21. 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(3):191-199.
22. 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(11):2043-2046. doi:10.1016/j.jacc.2005.05.098.
23. Liang KV, Hiniker AR, Williams 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 Card Fail*. 2006;12(9):707-714. doi:10.1016/j.cardfail.2006.08.210.
24. Rose EA, Gelijns AC, Moskowitz AJ, et al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med*. 2001;345(20):1435-1443. doi:10.1056/NEJMoa012175.
25. Cipolla CM, Grazi S, Rimondini A, et al. Changes in circulating norepinephrine with hemofiltration in advanced congestive heart failure. *Am J Cardiol*. 1990;66(12):987-994.
26. 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(1):49-56.
27. Costanzo MR, Guglin ME, Saltzberg MT, et al. Ultrafiltration versus intravenous diuretics for patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol*. 2007;49(6):675-683. doi:10.1016/j.jacc.2006.07.073.
28. Costanzo MR, Saltzberg MT, Jessup M, et al. Ultrafiltration is associated with fewer rehospitalizations than continuous diuretic infusion in patients with decompensated heart failure: results from UNLOAD. *J Card Fail*. 2010;16(4):277-284. doi:10.1016/j.cardfail.2009.12.009.
29. 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):1-4. doi:10.1111/j.1751-7133.2008.00037.x.
30. Abdallah JG, Schrier RW, Edelstein C, et al. Loop diuretic infusion increases thiazide-sensitive Na(+)/Cl(–)-cotransporter abundance: role of aldosterone. *J Am Soc Nephrol*. 2001;12(7):1335-1341.
31. 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(7):589-596. doi:10.1016/j.jacc.2008.05.068.
32. 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(7):597-599. doi:10.1016/j.jacc.2008.11.012.
33. Ross EA. Congestive renal failure: the pathophysiology and treatment of renal venous hypertension. *J Card Fail*. 2012;18(12):930-938. doi:10.1016/j.cardfail.2012.10.010.
34. 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 Card Fail*. 2012;18(3):176-182. doi:10.1016/j.cardfail.2011.12.009.
35. 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(3):265-272. doi:10.1161/circulationaha.109.933275.
36. Testani JM, Brisco MA, Chen J, et al. Timing of hemoconcentration during treatment of acute decompensated heart failure and subsequent survival: importance of sustained decongestion. *J Am Coll Cardiol*. 2013;62(6):516-524. doi:10.1016/j.jacc.2013.05.027.
37. Valika AA, Costanzo MR. The acute cardiorenal syndrome type I: considerations on physiology, epidemiology, and therapy. *Curr Heart Fail Rep*. 2014;11(4):382-392. doi:10.1007/s11897-014-0224-6.

38. 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(6):298-301. doi:10.1111/j.1751-7133.2008.00020.x.
39. 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(19):1906-1912. doi:10.1016/j.jacc.2012.08.957.
40. 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(3):145-153. doi:10.1159/000342457.
41. Singh P, Rifkin DE, Blantz RC. Chronic kidney disease: an inherent risk factor for acute kidney injury? *Clin J Am Soc Nephrol*. 2010;5(9):1690-1695. doi:10.2215/cjn.00830110.
42. Costanzo MR, Negoianu D, Fonarow GC, et al. Rationale and design of the Aquapheresis Versus Intravenous Diuretics and Hospitalization for Heart Failure (AVOID-HF) trial. *Am Heart J*. 2015;170(3):471-482. doi:10.1016/j.ahj.2015.05.019.
43. Costanzo MR, Chawla LS, Tumlin JA, et al. The role of early and sufficient isolated venovenous ultrafiltration in heart failure patients with pulmonary and systemic congestion. *Rev Cardiovasc Med*. 2013;14(2-4):e123-e133.
44. Costanzo MR, Negoianu D, Jaski BE, et al. Aquapheresis Versus Intravenous Diuretics and Hospitalizations for Heart Failure. *JACC Heart Fail*. 2016;4(2):95-105. doi:10.1016/j.jchf.2015.08.005.
45. Marenzi G, Muratori M, Cosentino ER, et al. Continuous ultrafiltration for congestive heart failure: the CUORE trial. *J Card Fail*. 2014;20(1):9-17. http://dx.doi.org/10.1016/j.cardfail.2013.11.004.
46. 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(14):1977-2016. doi:10.1161/circulationaha.109.192064.
47. 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(5):423-433. doi:10.1093/eurjhf/hfq045.
48. 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(4):963-968.
49. Stawicki SP, Braslow BM, Panebianco NL, et al. Intensivist use of hand-carried ultrasonography to measure IVC collapsibility in estimating intravascular volume status: correlations with CVP. *J Am Coll Surg*. 2009;209(1):55-61. doi:10.1016/j.jamcollsurg.2009.02.062.
50. Ronco C, Brendolan A, Bellomo R. Online monitoring in continuous renal replacement therapies. *Kidney Int Suppl*. 1999;72:S8-S14.
51. James KB, Troughton RW, Feldschuh J, et al. Blood volume and brain natriuretic peptide in congestive heart failure: a pilot study. *Am Heart J*. 2005;150(5):984. doi:10.1016/j.ahj.2005.07.031.
52. Katz SD. Blood volume assessment in the diagnosis and treatment of chronic heart failure. *Am J Med Sci*. 2007;334(1):47-52. doi:10.1097/MAJ.0b013e3180ca8c41.
53. Piccoli A, Nigrelli S, Caberlotto A, et al. Bivariate normal values of the bioelectrical impedance vector in adult and elderly populations. *Am J Clin Nutr*. 1995;61(2):269-270.
54. Piccoli A. Whole body–single frequency bioimpedance. *Contrib Nephrol*. 2005;149:150-161. doi:10.1159/000085478.
55. Larsen TR, Singh G, Velocci V, et al. Frequency of fluid overload and usefulness of bioimpedance in patients requiring intensive care for sepsis syndromes. *Proc (Bayl Univ Med Cent)*. 2016;29(1):12-15.
56. Ronco C, Kaushik M, Valle R, et al. Diagnosis and management of fluid overload in heart failure and cardio-renal syndrome: the "5B" approach. *Semin Nephrol*. 2012;32(1):129-141. doi:10.1016/j.semnephrol.2011.11.016.
57. Costanzo MR, Cozzolino M, Aspromonte N, et al. Extracorporeal ultrafiltration in heart failure and cardio-renal syndromes. *Semin Nephrol*. 2012;32(1):100-111. doi:10.1016/j.semnephrol.2011.11.013.
58. Maisel AS, Krishnaswamy P, Nowak RM, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med*. 2002;347(3):161-167. doi:10.1056/NEJMoa020233.
59. Januzzi JL Jr, Rehman SU, Mohammed AA, et al. Use of amino-terminal pro-B-type natriuretic peptide to guide outpatient therapy of patients with chronic left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2011;58(18):1881-1889. doi:10.1016/j.jacc.2011.03.072.
60. Savarese G, Trimarco B, Dellegrottaglie S, et al. Natriuretic peptide-guided therapy in chronic heart failure: a meta-analysis of 2,686 patients in 12 randomized trials. *PLoS ONE*. 2013;8(3):e58287. doi:10.1371/journal.pone.0058287.
61. 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(4):635-641. doi:10.1016/j.jacc.2003.09.044.
62. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med*. 2008;148(11):810-819.