Journal of the American College of Cardiology
© 2012 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 59, No. 24, 2012
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.10.910

STATE-OF-THE-ART PAPER

Diuretics and Ultrafiltration in Acute Decompensated Heart Failure

G. Michael Felker, MD, MHS, Robert J. Mentz, MD

Durham, North Carolina

Congestion and volume overload are the hallmarks of acute decompensated heart failure (ADHF), and loop diuretics have historically been the cornerstone of treatment. The demonstrated efficacy of loop diuretics in managing congestion is balanced by the recognized limitations of diuretic resistance, neurohormonal activation, and worsening renal function. However, the recently published DOSE (Diuretic Optimization Strategies Evaluation) trial suggests that previous concerns about the safety of high-dose diuretics may not be valid. There has been a growing interest in alternative strategies to manage volume retention in ADHF with improved efficacy and safety profiles. Peripheral venovenous ultrafiltration (UF) represents a potentially promising approach to volume management in ADHF. Small studies suggest that UF may allow for more effective fluid removal compared with diuretics, with improved quality of life and reduced rehospitalization rates. However, further investigation is needed to completely define the role of UF in patients with ADHF. This review summarizes available data on the use of both diuretics and UF in ADHF patients and identifies challenges and unresolved questions for each approach. (J Am Coll Cardiol 2012;59:2145–53) © 2012 by the American College of Cardiology Foundation

Heart failure (HF) is a major and growing public health problem worldwide with high morbidity, mortality, and cost (1). Hospitalizations for acute decompensated heart failure (ADHF) have increased over time, and costs related to hospitalization account for ~75% of the total cost of HF care (2). Despite therapeutic advances in the care of chronic HF, the prognosis of patients with ADHF remains poor, with an in-hospital mortality rate of ~4% (3), 30-day rehospitalization rates of 23% (4), and a 6-month mortality rate approaching 20% in advanced HF (5)—with all event rates notably higher than those of myocardial infarction. Fluid retention and congestion are responsible for 90% of HF hospitalizations (1,3), and greater severity of congestion is associated with worse outcomes (6). Intravenous loop diuretics remain the first-line therapy for ADHF and are currently prescribed for ~90% of hospitalized ADHF patients (3). Despite the ubiquitous use of these agents, there are persistent uncertainties about appropriate dosing and the overall safety profile (7,8). Even with diuretic therapy, ~40% of hospitalized HF patients are discharged with unresolved congestion (9), with increased rehospitalization (10) and mortality (11) rates. There has been an increasing focus on an evidence-based approach to diuretic use in ADHF, as well as investigating alternative strategies to manage volume retention. Peripheral venovenous ultrafiltration (UF) has emerged as a potentially promising alternative to diuretic therapy in ADHF (12). This review summarizes the currently available data on the use of both loop diuretics and UF in ADHF and identifies challenges and unresolved questions for each approach.

Loop Diuretics in ADHF

Pharmacology. Loop diuretics inhibit the $Na^+/2Cl^-/K^+$ cotransporter in the thick ascending loop of Henle, resulting in decreased urine sodium and chloride reabsorption with natriuresis and diuresis. The 3 commonly used loop diuretics all work via these same mechanisms, although pharmacologic differences may have clinical importance (Table 1) (13). The greater bioavailability of bumetanide and torsemide may offer more predictable diuresis, and the increased half-life of torsemide in the setting of renal, hepatic, and/or cardiac dysfunction may be advantageous for extended diuresis. The data comparing the loop diuretics are limited to small-scale, chronic HF studies with short follow-up and underuse of contemporary therapy as recently reviewed (14). These hypothesis-generating studies suggested potential benefits with torsemide compared with furosemide on neurohormonal activation, left ventricular remodeling, and fibrotic changes with resultant reduced hospitalizations, improved symptoms, and potentially reduced mortality (14). These findings would need to be confirmed in contemporary, adequately powered clinical trials.

Given the need for rapid onset of action, loop diuretics are typically given intravenously for hospitalized ADHF patients.

From the Division of Cardiology, Department of Medicine, Duke University School of Medicine, Durham, North Carolina. Both authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received September 5, 2011; revised manuscript received October 11, 2011, accepted October 17, 2011.

Abbreviations and Acronyms

ADHF = acute decompensated heart failure
HF = heart failure
HSS = hypertonic saline solution
IV = intravenous
RAAS = renin-angiotensin-aldosterone system
UF = ultrafiltration
WRF = worsening renal function

Intravenous (IV) administration of an effective dose furosemide typically results in a diuretic effect within 30 min that peaks at 1 h (14). In HF, the dose–response curve shifts downward and to the right, thereby necessitating a higher dose to achieve the same effect (Fig. 1) (8,13). The sigmoid-shaped dose–response relationship demonstrates the importance of attaining a diuretic concentration on the steep part of the curve between the minimal effective dose and dose ceiling. With renal insufficiency, as seen in >50% of ADHF patients (15), organic anions compete with receptor sites for tubular transporters (16) and further increase dose requirements.

Although loop diuretics are commonly given by intermittent IV bolus, there are potential benefits of continuous infusion. Continuous infusion results in a more constant delivery of diuretic to the tubule, potentially reducing a post-diuretic "rebound" sodium retention and maintaining more consistent diuresis. Although a meta-analysis suggested greater urine output, shorter length of hospital stay, less renal impairment, and lower mortality rate with continuous infusion compared with intermittent bolus dosing (17), the recently published DOSE (Diuretic Optimization Strategies Evaluation) trial called these findings into question, as discussed below (18).

Efficacy. Loop diuretic use in ADHF generally improves dyspnea and decreases ventricular filling pressures (Fig. 2) (7,19). Loop diuretics may induce the synthesis of prostaglandins with vascular smooth muscle relaxation resulting in renal and pulmonary vasodilation (20,21). Although decades of clinical experience suggest that loop diuretics are generally effective at managing congestion in ADHF, recent studies suggested that the lack of adequate decongestion is more common than previously appreciated (22,23). The largest ADHF trial to date, the ASCEND-HF (Acute Studies of Clinical Effectiveness of Nesiritide in Subjects with Decompensated Heart Failure) trial (N = 7,141), demonstrated that standard ADHF care resulted in improved dyspnea at 24 h in 66% of patients (24). The lack of adequate symptom relief with diuretics has been associated with longer hospital stays and increased mortality, underscoring the importance of effective decongestion in improving outcomes in ADHF (22,23).

Safety. Observational studies have shown associations between high doses of loop diuretics and adverse clinical outcomes (7,25–27). These observations are confounded by the fact that patients receiving higher doses of diuretics tend to have greater disease severity or comorbidity, making it impossible to establish whether the relationship between diuretic dose and outcomes is causal. Potential mechanisms for worse outcomes with loop diuretics include stimulation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system (28–30), electrolyte disturbances, and deterioration of renal function (31,32) (Fig. 2). A recent analysis of the BEST (Beta-blocker Evaluation of Survival Trial) found that worsened mortality in association with high-dose loop diuretics was primarily limited to those patients with elevated blood urea nitrogen, suggesting a role for neurohormonal activation in observed increase mortality with loop diuretics (33). An animal study using a porcine

Table 1 Pharmacokinetics of the Loop Diuretics

Property	Furosemide	Bumetanide	Torsemide
Relative IV potency, mg	40	1	20
Bioavailability, %	10–100 (average, 50)	80–100	80–100
Oral to intravenous conversion	2:1	1:1	1:1
Initial outpatient total daily oral dose, mg	20–40	0.5–1	5–10
Maintenance outpatient total daily oral dose, mg	40–240	1–5	10–200
Maximum daily intravenous dose, mg	400–600	10	200
Onset, min			
Oral	30–60	30–60	30–60
Intravenous	5	2–3	10
Peak serum concentration after oral administration, h	1	1–2	1
Affected by food	Yes	Yes	No
Metabolism	50% renal conjugation	50% hepatic	80% hepatic
Half-life, h			
Normal	1.5–2	1	3–4
Renal dysfunction	2.8	1.6	4–5
Hepatic dysfunction	2.5	2.3	8
Heart failure	2.7	1.3	6
Average duration of effect, h	6–8	4–6	6–8
Approximate cost for oral 30-day supply (community pharmacy), $	4	4	19–23

Adapted, with permission, from Felker (13) and Wargo and Banta (14).

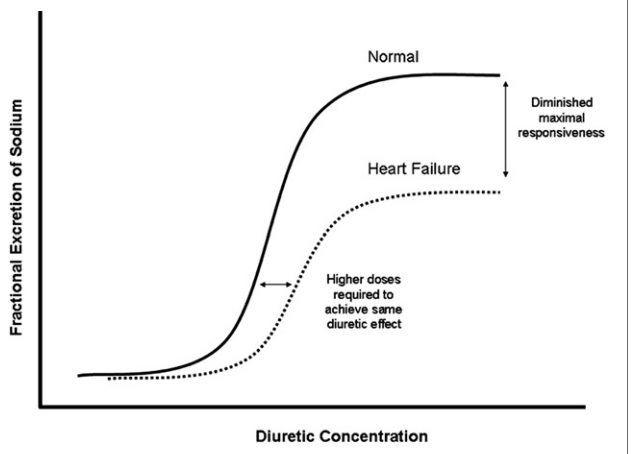

Figure 1 **Schematic of Dose–Response Curve of Loop Diuretics in Heart Failure Patients Compared With Normal Controls**

In heart failure patients, higher doses are required to achieve a given diuretic effect and the maximal effect is blunted. Adapted, with permission, from Ellison (8) and reprinted, with permission, from Felker (13).

HF model showed that treatment with furosemide resulted in an increased progression of left ventricular systolic dysfunction (34).

Of particular interest is the association of higher diuretic dosing with worsening renal function (WRF) during ADHF hospitalization because WRF characterized by changes in creatinine and/or estimated glomerular filtration rate has been shown to be a predictor of poor outcomes (7,15). More recent data from several studies, however, have suggested that transient WRF during acute HF therapy may not affect post-discharge outcomes (35,36). Given that persistent congestion is itself a predictor of both WRF (37) and adverse outcomes (38), it would appear that transient WRF may be a reasonable trade-off in exchange for better decongestion. Understanding the optimal balance between the benefits of decongestion and the potential adverse effects of diuretics served as the rationale for the DOSE trial.

The DOSE trial. There is limited evidence to guide diuretic use as reflected in practice guidelines in which diuretic therapy is given a class I recommendation with a level of evidence based on expert opinion (39–41). The recently published DOSE trial is the largest prospective, double blind, randomized ADHF trial to evaluate initial diuretic strategies (18). Using a 2 × 2 factorial design, the DOSE trial randomized 308 ADHF patients to IV furosemide given as twice-daily boluses or continuous infusion and to either a low dose (IV dose numerically equivalent to the patient's oral dose) or a high dose (2.5 times oral dose given intravenously) strategy. There was no significant difference in either of the co-primary endpoints of global assessment of symptoms (Fig. 3A) or change in serum creatinine over 72 h with diuretic administration by bolus or continuous infusion or with a low- versus a high-dose strategy. However, patients randomized to the higher dose strategy had more favorable outcomes with regard to several secondary measures, including relief of dyspnea, change in weight, and net fluid loss. These potential benefits were balanced by greater changes in renal function (Fig. 3B). Although the mean change in creatinine from baseline to 72 h was not significantly different between the low- and high-dose strategy, the high-dose approach was associated with a significantly higher proportion of patients experiencing transient WRF (increase in creatinine >0.3 mg/dl). Despite these changes in renal function, the higher dose group had fewer serious adverse events and no evidence of worse 60-day outcomes. Taken as a whole, the data suggest that higher doses of diuretics are likely to be more efficacious in relieving congestion than a low-dose strategy, at the cost of transient WRF that does not appear to have long-term consequences.

Challenges of Diuretic Therapy

Diuretic resistance. In ADHF, diuretics may fail to adequately control salt and water retention despite dose escalation. This concept of diuretic resistance captures an ADHF subpopulation at high risk of morbidity and mortality (42). Several mechanisms contribute to this progressive diminution of loop diuretic efficacy (43). First, loop diuretics are "threshold drugs," so an adequate dose is needed to achieve therapeutic effect. The shift of the dose–response curve in HF implicates insufficient dosing as a common cause of a lack of diuretic response. Differentiating diuretic resistance versus inadequate dosing is a well-recognized problem and is an area of ongoing research (44). Dose escalation beyond a patient's previously recognized dose ceiling or a dose approaching the maximum recommended daily dose without incremental improvement in diuresis suggests diuretic resistance. An additional mechanism for diuretic resistance involves the "braking phenomenon" in which long-term loop diuretic administration results in a reduced natriuretic response. This phenomenon occurs due to a relative or absolute contraction of the extracellular fluid volume, resulting in reduced delivery of solute to the proximal tubule via the RAAS and sympathetic nerve–mediated mechanisms (45), as well as enhanced distal nephron solute reabsorption via adaptive epithelial hypertrophy and hyperfunction (46). Third, when the diuretic concentration in the tubular fluid decreases to below a therapeutic level, there is a period of post-diuretic sodium retention or "rebound" (8). Infrequent dosing may therefore lead to sodium retention that exceeds natriuresis, especially if dietary sodium intake is not restricted. Therefore, loop diuretics are generally more effective when given in several divided doses or continuously to limit this "rebound" effect.

Strategies for overcoming diuretic resistance. For patients with volume overload who are refractory to escalating doses of IV diuretics, several treatment options exist to try and enhance diuretic efficacy. Thiazide diuretics can be

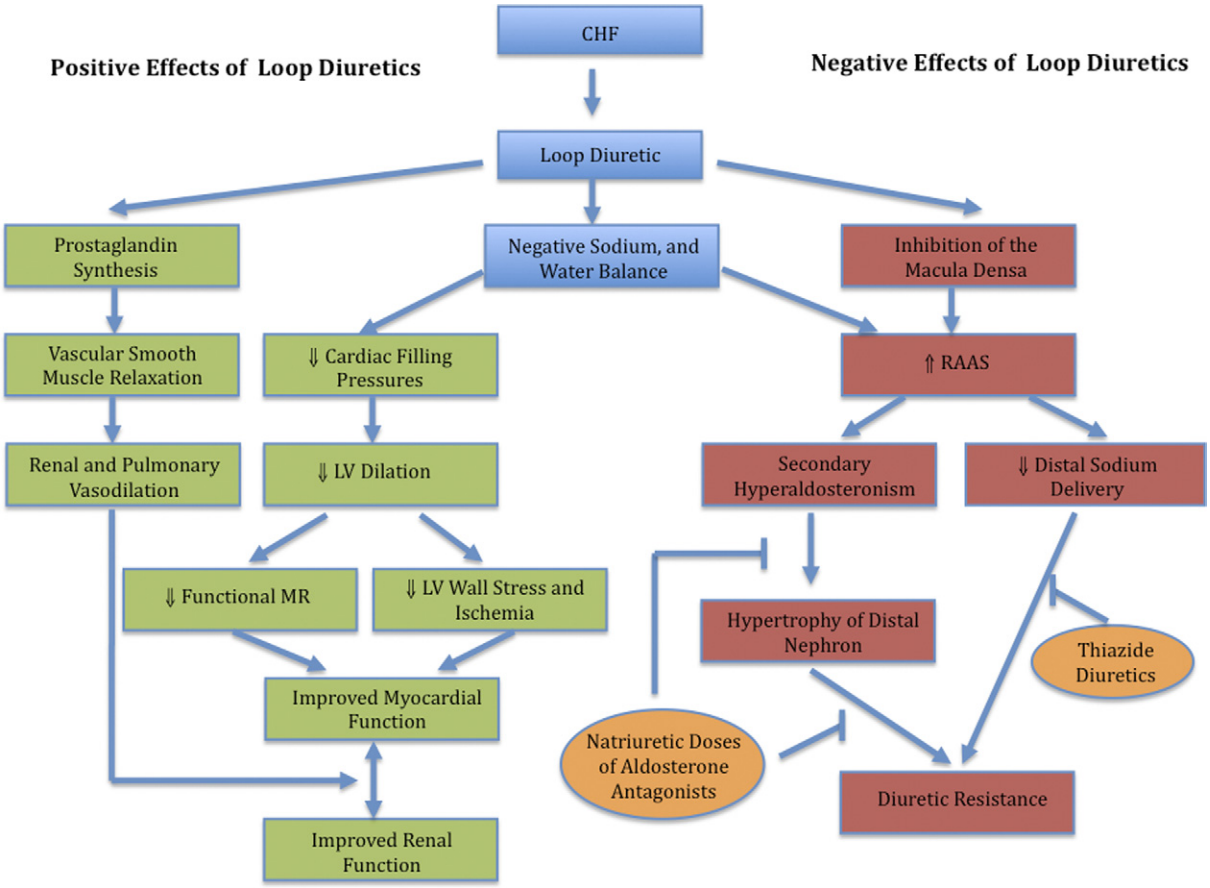

Figure 2 **Diuretic Mechanisms**

Proposed positive and negative effects of loop diuretics as well as sites of action for thiazide diuretics and natriuretic doses of aldosterone antagonists.
CHF = congestive heart failure; LV = left ventricular; MR = mitral regurgitation; RAAS = renin-angiotensin-aldosterone system. Adapted, with permission, from Schrier (7).

effective adjuncts to loop diuretics (43). Thiazides are typically given as a single oral dose 1 h before loop diuretic dosing. Although this strategy can often be effective in overcoming diuretic resistance, careful monitoring of fluid status and serum electrolytes is critical. The combination of thiazides and loop diuretics can induce severe volume depletion or electrolyte disturbances including hypokalemia and hypomagnesemia with resultant increased risk of arrhythmias.

Aldosterone antagonists used at natriuretic doses may be another approach to overcome diuretic resistance (47). Although these agents are technically diuretics, they generally have little diuretic effect in patients with chronic HF at the standard doses (48). Much higher doses of spironolactone have been used in patients with cirrhosis, and small studies suggest that higher doses may be an adjunct to loop diuretics in achieving natriuresis (47). Because loop diuretics may worsen RAAS activation and secondary hyperaldosteronism, improved blockade of the sodium-retaining effect of aldosterone may enhance natriuresis (Fig. 2). Given the limited safety data available with this approach, such a strategy should only be undertaken with great care and close monitoring of volume status and electrolytes with concern for hyperkalemia.

Several HF trials have demonstrated positive results incorporating hypertonic saline solution (HSS) with loop diuretics (49–51). The largest of these was a 1,771-patient study of ADHF patients with diuretic resistance who were randomized to HSS (150 ml) plus twice-daily high-dose IV furosemide (250 mg) and a moderate sodium restriction (120 mmol) compared with the same diuretic regimen without HSS and a low sodium diet (80 mmol) (50). Those receiving HSS showed a significant increase in diuresis and shorter length of stay (3.5 vs. 5.5 days; $p < 0.0001$) with a favorable effect on creatinine clearance. During a mean follow-up of 57 months, the HSS and moderate sodium restriction group had reduced readmission (18.5% vs. 34.2%; $p < 0.0001$) and mortality (12.9% vs. 23.8%; $p < 0.0001$) rates. Hypothesized mechanisms for beneficial effects of low-volume HSS include restoration of effective arterial volume with improved neurohormonal inhibition and renal hemodynamic improvements as well as decreased

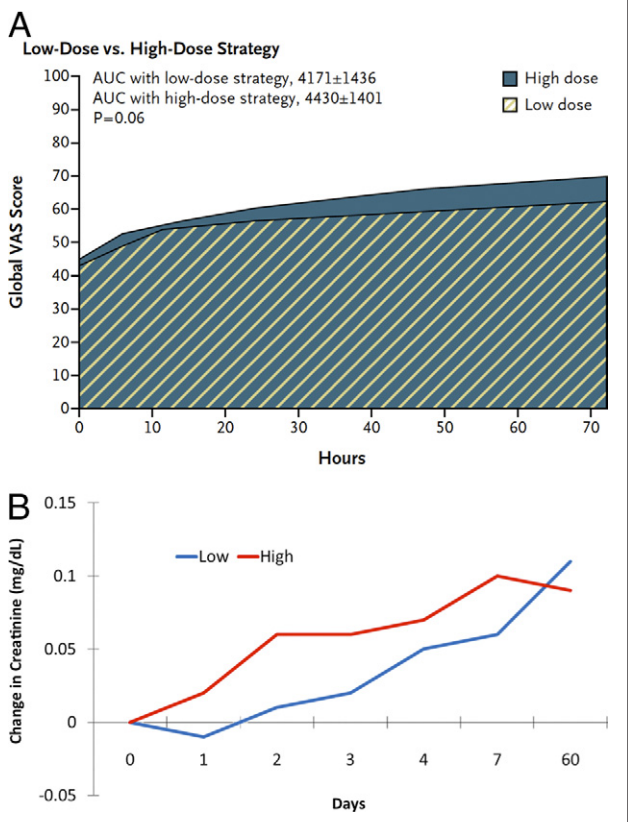

Figure 3 **Patients' Global Assessment of Symptoms (VAS) During the 72-h Study Treatment Period and Changes in Serum Creatinine Over Time**

(A) Patients' global assessment of symptoms was quantified as the area under the curve (AUC) of serial assessments from baseline to 72 h. Mean (± SD) AUCs are shown for the group that received a low dose of the diuretic compared with the group that received a high dose. **(B)** The mean change in serum creatinine level over the course of the study is shown for the group that received a low dose of the diuretic compared with the group that received a high dose. VAS = visual analog scale. Reprinted, with permission, from Felker et al. (18).

afterload, improved cardiac contractility, and enhanced diuretic responsiveness (50). These mechanisms are supported by data from small studies demonstrating that liberalization of dietary sodium in compensated HF patients may attenuate counterproductive neuroendocrine and hemodynamic responses, as recently reviewed (52). Given that ADHF patients have an excess of total body sodium, the efficacy of this counterintuitive therapeutic strategy as a method to suppress the body's maladaptive responses and facilitate diuresis will need to be confirmed in more carefully controlled trials (53). Furthermore, how HSS administration would compare with alternative methods to improve intravascular volume such as albumin administration requires further investigation (54).

Early studies showed that low-dose dopamine increases the glomerular filtration rate and renal blood flow in stable HF patients (55,56), but contemporary randomized studies are generally lacking. The DAD-HF (Dopamine in Acute Decompensated Heart Failure) study investigated 60 patients randomized to high-dose furosemide (continuous infusion at 20 mg/h) or low-dose furosemide plus low-dose dopamine (continuous infusions at 5 mg/h and 5 μg/kg/min, respectively) for 8 h (57). WRF occurred more frequently in the high-dose diuretic arm (30% vs. 9%; p = 0.04), but there was a similar length of stay and 60-day mortality/rehospitalization. Overall, a low-dose loop diuretic combined with low-dose dopamine was as effective as high-dose furosemide infusion in terms of urine output and dyspnea relief with an improved renal function profile. However, based on the DOSE trial, the higher incidence of WRF in the nondopamine arm could have been attributed to the high-dose diuretic regimen rather than a benefit from dopamine in the low-dose diuretic arm. The ongoing ROSE-AHF (Renal Optimization Strategies Evaluation in Acute Heart Failure, NCT01132846) study comparing low-dose nesiritide, low-dose dopamine, and placebo as adjuncts to loop diuretics in patients with ADHF and renal dysfunction will shed light on the relative efficacy and safety of these approaches.

UF in the Management of HF

Ultrafiltration allows for the extracorporeal removal of plasma water from whole blood across a semipermeable membrane in response to a transmembrane pressure gradient. UF in its different forms has been used for decades in refractory edema (58). The recent development of veno-venous peripheral UF has positioned UF on the forefront as an alternative to loop diuretics in ADHF. Contemporary UF devices allow for the removal of fluid at the bedside using peripheral IV access without specialized personnel (59).

Pathophysiology of UF

Ultrafilitration offers a mechanism for relatively rapid and controlled treatment of volume overload, with volume removal rates as high as 500 ml/h. A potential advantage of UF over loop diuretics is that the ultrafiltrate is isotonic, whereas the urinary output with loop diuretics is hypotonic, and therefore UF removes more sodium (and less potassium) than diuretics for an equivalent volume loss (60). If fluid removal does not exceed the interstitial fluid mobilization rate of approximately 15 ml/min, then the intravascular volume can be preserved with UF, potentially interrupting the vicious cycle of neurohormonal activation and renal impairment that can occur with loop diuretics (61). This hypothesis is supported by data demonstrating that patients receiving UF have lower plasma renin, norepinephrine and aldosterone levels as long as 90 days after treatment compared with those receiving diuretics (62). Most studies investigating neurohormonal activation generally preceded the routine use of beta-blockers or contemporary angiotensin-converting enzyme inhibitors, and the potential neurohormonal benefits of UF in the contemporary ADHF patient are ill-defined. Nonetheless, small studies suggest that UF improves pulmonary and

peripheral edema, lung function, and hemodynamics without adverse effects on renal function (61–64). Favorable hemodynamic changes with UF may result in improved renal function and restoration of diuretic responsiveness (63,65). The avoidance of electrolyte abnormalities may also account for improved outcomes (12,66).

Practical Aspects of UF Therapy

Venovenous UF can be performed via either central or peripheral vascular access as long as there are 2 catheters or 2 lumens that can provide 10 to 40 ml/min of blood flow. The UF procedure uses a transportable UF console along with a disposable, single-use extracorporeal blood circuit (Fig. 4) (67). Full anticoagulation therapy with continuous infusion of heparin is recommended to preserve filter function. Fluid removal rates are set by the provider and range from 10 to 500 ml/h; typical rates for volume removal in clinical studies have been approximately 250 ml/h (12,68). The fluid removal rate is re-evaluated over time to confirm adequate plasma refill using serial clinical parameters and potentially serial hematocrit measurements (63). Care must be taken that removal of intravascular volume does not exceed the capillary refill rate because this can lead to further RAAS activation, hypotension, and renal injury (61,69). Typical treatments last for 24 h, although more extended periods are possible. The benefits of repeated UF sessions either during hospitalizations or as an outpatient management strategy are unknown. Patients with poor venous access, hypercoagulable states, hypotension, advanced renal disease, and cardiogenic shock and those requiring inotropic support are generally not suitable for UF therapy.

Outcomes with UF in HF. Early studies were of small sample size, included highly selected patient populations, and had short follow-up (61,62,64). The impact of UF on symptoms, renal function, and post-discharge outcomes was recently examined in the RAPID-CHF (Relief for Acutely

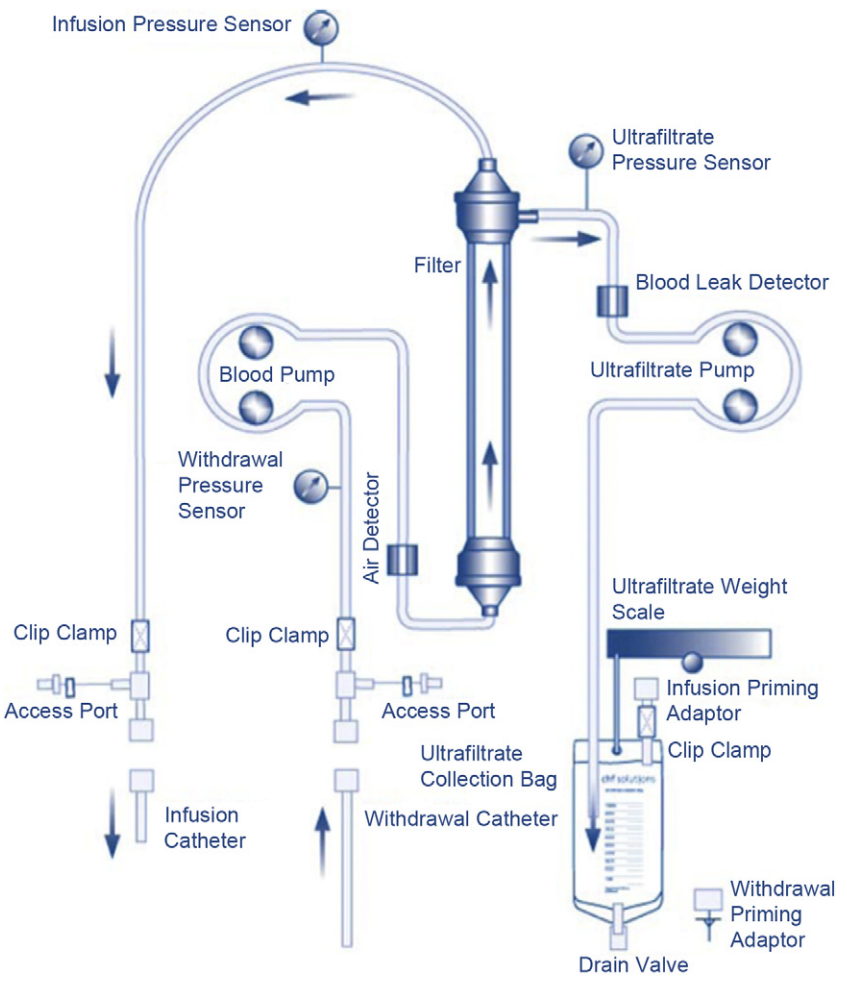

Figure 4 Acute Decompensated Heart Failure Ultrafiltration System

Ultrafiltration system for salt and water removal using a low volume of extracorporeal blood through peripheral or central venous access (CHF Solutions Inc., Minneapolis, Minnesota). Reprinted, with permission, from Mather and Konstam (67).

Fluid-Overloaded Patients with Decompensated Congestive Heart Failure) and UNLOAD (Ultrafiltration vs. Intravenous Diuretics for Patients Hospitalized with Acute Decompensated Heart Failure) trials.

The RAPID-CHF trial was a small proof-of-concept trial of 40 patients with ADHF randomized to a single 8-h session of UF or to usual care (68). For the primary endpoint of weight loss at 24 h, there was no significant difference between UF and usual care. However, fluid removal after 24 h was significantly greater with UF. Dyspnea and HF symptoms at 48 h were also significantly improved in the UF group compared with those receiving usual care.

The UNLOAD trial is the largest trial to date investigating UF in ADHF (12). This unblinded trial randomized 200 patients with ADHF to either UF or loop diuretic therapy within 24 h of hospitalization. The UNLOAD trial studied UF as primary therapy (i.e., the protocol did not require failure of initial diuretic therapy for entry). The co-primary endpoints of the UNLOAD trial were weight loss and dyspnea relief at 48 h. The UF group had greater weight loss (5.0 ± 3.1 kg vs. 3.1 ± 3.5 kg; $p = 0.001$), but there was no difference in the patient-reported outcome of dyspnea. Notably, the UNLOAD trial showed a decrease in rehospitalization for HF with UF compared with diuretic therapy (hazard ratio: 0.56; $p = 0.04$) (Fig. 5). There was significantly less hypokalemia with UF compared with diuretics, and other safety parameters (including serum creatinine change) were similar in the 2 study arms. Although the potential effect of primary UF on reduction of HF rehospitalization is intriguing, this must be balanced by the recognition that this was a secondary endpoint and based on a relatively small number of events (16 of 86 UF patients vs. 28 of 87 usual care patients; $p = 0.04$). Furthermore, this small, unblinded study with short follow-up may have been confounded by unintentional bias because HF rehospitalizations were investigator reported, and criteria for rehospitalization were not presented.

The economic impact of UF as an initial strategy for ADHF remains uncertain. Although up-front costs may be greater with UF than with diuresis, total longitudinal costs could be lower if length of hospital stay is reduced and/or rehospitalization rates are decreased (12,66). A cost-consequences decision model analysis found that despite a reduction in rehospitalization with UF, it was unlikely to result in costs savings from a societal level (70). However, these calculations were based on recently developed UF devices and proprietary supplies. Another recent review on the financial implications of UF in HF highlighted the high costs of disposable materials and staff training (71). Production of lower cost UF supplies and streamlined training could shift the cost–benefit analysis. Further analysis of the economic aspects of UF therapy will be an important step in defining the role for UF before broad clinical application.

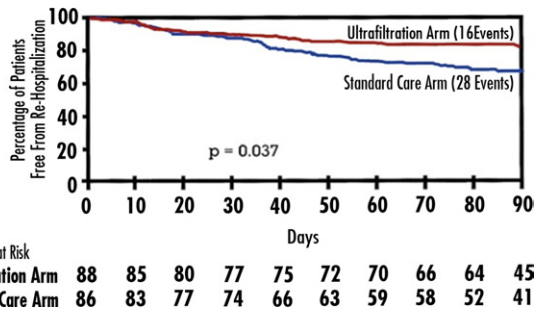

Figure 5 Freedom From Heart Failure Rehospitalization

Kaplan-Meier estimate of freedom from rehospitalization for heart failure within 90 days after discharge in the ultrafiltration **(red line)** and standard care **(blue line)** groups. Reprinted, with permission, Costanzo et al. (12).

At present, current guidelines recommend UF therapy only for patients who have not responded to initial medical therapy (Class IIa, Level of Evidence: B) (39,40). The reduction in rehospitalization with UF therapy as seen in the UNLOAD trial will need to be confirmed in larger, appropriately powered studies before primary UF therapy can be considered a first-line treatment. The role of UF as a treatment for the so-called cardiorenal syndrome is also currently under investigation in the National Institutes of Health–sponsored CARRESS study (Effectiveness of Ultrafiltration in Treating People With Acute Decompensated Heart Failure and Cardiorenal Syndrome, NCT00608491), which is randomizing patients with ADHF, WRF, and persistent volume overload to a strategy of UF versus stepped pharmacological management with a primary endpoint of the change in serum creatinine and change in weight considered as a bivariate endpoint at 96 h.

Conclusions

Congestion and volume retention are the hallmark of HF, and loop diuretic therapy plays a central role in their treatment. Although many unanswered questions remain about the best approach for using diuretics, their demonstrated efficacy in relieving congestion and the long clinical experience suggest that they will remain an important part of the ADHF armamentarium. The results of the DOSE trial suggest that previous concerns about the safety of high-dose diuretics may not be valid, especially if more effective decongestion can be achieved. Peripheral veno-venous UF represents one of the most promising novel approaches to volume management in ADHF. Potentially, UF may allow for more effective removal of sodium and fluid without the electrolyte abnormalities or neurohormonal activation seen with diuretics, with improved quality of life and reduced rehospitalization rates. The optimal method for achieving successful decongestion while minimizing changes in renal function and neurohormonal activation remains an area of intensive ongoing research, which will provide greater insight into the best practices for the management of ADHF.

Reprint requests and correspondence: Dr. G. Michael Felker, Duke Clinical Research Institute, 2400 Pratt Street, Room 0311, Terrace Level, Durham, North Carolina 27705. E-mail: michael.felker@duke.edu.

REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics--2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119:e21–181.
2. Fang J, Mensah GA, Croft JB, Keenan NL. Heart failure-related hospitalization in the U.S., 1979 to 2004. J Am Coll Cardiol 2008;52:428–34.
3. Adams KF Jr., Fonarow GC, Emerman CL, et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J 2005;149:209–16.
4. Ross JS, Chen J, Lin Z, et al. Recent national trends in readmission rates after heart failure hospitalization. Circ Heart Fail 2010;3:97–103.
5. O'Connor CM, Hasselblad V, Mehta RH, et al. Triage after hospitalization with advanced heart failure: the ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) risk model and discharge score. J Am Coll Cardiol 2010;55:872–8.
6. 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;12:423–33.
7. Schrier RW. Role of diminished renal function in cardiovascular mortality: marker or pathogenetic factor? J Am Coll Cardiol 2006;47:1–8.
8. Ellison DH. Diuretic therapy and resistance in congestive heart failure. Cardiology 2001;96:132–43.
9. Gheorghiade M, Filippatos G. Reassessing treatment of acute heart failure syndromes: the ADHERE Registry. Eur Heart J Suppl 2005;7:B13–9.
10. Jain P, Massie BM, Gattis WA, Klein L, Gheorghiade M. Current medical treatment for the exacerbation of chronic heart failure resulting in hospitalization. Am Heart J 2003;145:S3–17.
11. Androne AS, Katz SD, Lund L, et al. Hemodilution is common in patients with advanced heart failure. Circulation 2003;107:226–9.
12. 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;49:675–83.
13. Felker GM. Diuretic management in heart failure. Congest Heart Fail 2010;16 Suppl 1:S68–72.
14. Wargo KA, Banta WM. A comprehensive review of the loop diuretics: should furosemide be first line? Ann Pharmacother 2009;43:1836–47.
15. Heywood JT, Fonarow GC, Costanzo MR, Mathur VS, Wigneswaran JR, Wynne J. 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;13:422–30.
16. De Bruyne LK. Mechanisms and management of diuretic resistance in congestive heart failure. Postgrad Med J 2003;79:268–71.
17. Salvador DR, Rey NR, Ramos GC, Punzalan FE. Continuous infusion versus bolus injection of loop diuretics in congestive heart failure. Cochrane Database Syst Rev 2005:CD003178.
18. Felker GM, Lee KL, Bull DA, et al. Diuretic strategies in patients with acute decompensated heart failure. N Engl J Med 2011;364:797–805.
19. Cody RJ. Clinical trials of diuretic therapy in heart failure: research directions and clinical considerations. J Am Coll Cardiol 1993;22:165A–71A.
20. Dikshit K, Vyden JK, Forrester JS, Chatterjee K, Prakash R, Swan HJ. Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. N Engl J Med 1973;288:1087–90.
21. Dormans TP, Pickkers P, Russel FG, Smits P. Vascular effects of loop diuretics. Cardiovasc Res 1996;32:988–97.
22. Metra M, Cleland JG, Weatherley BD, et al. Dyspnoea in patients with acute heart failure: an analysis of its clinical course, determinants, and relationship to 60-day outcomes in the PROTECT pilot study. Eur J Heart Fail 2010;12:499–507.
23. Metra M, Teerlink JR, Felker GM, et al. Dyspnoea and worsening heart failure in patients with acute heart failure: results from the Pre-RELAX-AHF study. Eur J Heart Fail 2010;12:1130–9.
24. O'Connor CM, Starling RC, Hernandez AF, et al. Effect of nesiritide in patients with acute decompensated heart failure. N Engl J Med 2011;365:32–43.
25. Domanski M, Norman J, Pitt B, Haigney M, Hanlon S, Peyster E. Diuretic use, progressive heart failure, and death in patients in the Studies Of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol 2003;42:705–8.
26. Hasselblad V, Gattis Stough W, Shah MR, et al. Relation between dose of loop diuretics and outcomes in a heart failure population: results of the ESCAPE trial. Eur J Heart Fail 2007;9:1064–9.
27. Cooper HA, Dries DL, Davis CE, Shen YL, Domanski MJ. Diuretics and risk of arrhythmic death in patients with left ventricular dysfunction. Circulation 1999;100:1311–5.
28. He XR, Greenberg SG, Briggs JP, Schnermann J. Effects of furosemide and verapamil on the NaCl dependency of macula densa-mediated renin secretion. Hypertension 1995;26:137–42.
29. Bayliss J, Norell M, Canepa-Anson R, Sutton G, Poole-Wilson P. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. Br Heart J 1987;57:17–22.
30. Francis GS, Siegel RM, Goldsmith SR, Olivari MT, Levine TB, Cohn JN. Acute vasoconstrictor response to intravenous furosemide in patients with chronic congestive heart failure. Activation of the neurohumoral axis. Ann Intern Med 1985;103:1–6.
31. Brater DC. Diuretic therapy. N Engl J Med 1998;339:387–95.
32. Gottlieb SS, Skettino SL, Wolff A, et al. Effects of BG9719 (CVT-124), an A1-adenosine receptor antagonist, and furosemide on glomerular filtration rate and natriuresis in patients with congestive heart failure. J Am Coll Cardiol 2000;35:56–9.
33. Testani JM, Cappola TP, Brensinger CM, Shannon RP, Kimmel SE. Interaction between loop diuretic-associated mortality and blood urea nitrogen concentration in chronic heart failure. J Am Coll Cardiol 2011;58:375–82.
34. McCurley JM, Hanlon SU, Wei SK, Wedam EF, Michalski M, Haigney MC. Furosemide and the progression of left ventricular dysfunction in experimental heart failure. J Am Coll Cardiol 2004;44:1301–7.
35. Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure. J Card Fail 2010;16:541–7.
36. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation 2010;122:265–72.
37. 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;53:589–96.
38. Stevenson LW, Zile M, Bennett TD, et al. Chronic ambulatory intracardiac pressures and future heart failure events. Circ Heart Fail 2010;3:580–7.
39. 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.
40. 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 Heart J 2008;29:2388–442.
41. Executive summary: HFSA 2006 Comprehensive Heart Failure Practice Guideline. J Card Fail 2006;12:10–38.
42. Neuberg GW, Miller AB, O'Connor CM, et al. Diuretic resistance predicts mortality in patients with advanced heart failure. Am Heart J 2002;144:31–8.

43. Jentzer JC, DeWald TA, Hernandez AF. Combination of loop diuretics with thiazide-type diuretics in heart failure. J Am Coll Cardiol 2010;56:1527–34.
44. Ohtani T, Felker GM, McNulty SE, LeWinter MM, Braunwald E, Redfield MM. Plasma Renin Activity (PRA) Predicts Diuretic Resistance in Acute Heart Failure Patients: An Ancillary Study of the Diuretic Optimization Strategies Evaluation in Acute Heart Failure (DOSE-AHF). J Card Fail 2011;17:S25–6.
45. Loon NR, Wilcox CS, Unwin RJ. Mechanism of impaired natriuretic response to furosemide during prolonged therapy. Kidney Int 1989; 36:682–9.
46. Kaissling B, Bachmann S, Kriz W. Structural adaptation of the distal convoluted tubule to prolonged furosemide treatment. Am J Physiol 1985;248:F374–81.
47. Bansal S, Lindenfeld J, Schrier RW. Sodium retention in heart failure and cirrhosis: potential role of natriuretic doses of mineralocorticoid antagonist? Circ Heart Fail 2009;2:370–6.
48. Pitt B, Zannad F, Remme WJ, et al. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341:709–17.
49. Paterna S, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as a bolus, in refractory congestive heart failure. Eur J Heart Fail 2000;2:305–13.
50. Paterna S, Fasullo S, Parrinello G, et al. Short-term effects of hypertonic saline solution in acute heart failure and long-term effects of a moderate sodium restriction in patients with compensated heart failure with New York Heart Association class III (Class C) (SMAC-HF Study). Am J Med Sci 2011;342:27–37.
51. Licata G, Di Pasquale P, Parrinello G, et al. Effects of high-dose furosemide and small-volume hypertonic saline solution infusion in comparison with a high dose of furosemide as bolus in refractory congestive heart failure: long-term effects. Am Heart J 2003;145:459–66.
52. Liszkowski M, Nohria A. Rubbing salt into wounds: hypertonic saline to assist with volume removal in heart failure. Curr Heart Fail Rep 2010;7:134–9.
53. Drazner MH, Palmer BF. Hypertonic saline: a novel therapy for advanced heart failure? Am Heart J 2003;145:377–9.
54. Arques S, Ambrosi P. Human serum albumin in the clinical syndrome of heart failure. J Card Fail 2011;17:451–8.
55. Ungar A, Fumagalli S, Marini M, et al. Renal, but not systemic, hemodynamic effects of dopamine are influenced by the severity of congestive heart failure. Crit Care Med 2004;32:1125–9.
56. Elkayam U, Ng TM, Hatamizadeh P, Janmohamed M, Mehra A. Renal Vasodilatory Action of Dopamine in Patients With Heart Failure: Magnitude of Effect and Site of Action. Circulation 2008; 117:200–5.
57. Giamouzis G, Butler J, Starling RC, et al. Impact of dopamine infusion on renal function in hospitalized heart failure patients: results of the Dopamine in Acute Decompensated Heart Failure (DAD-HF) Trial. J Card Fail 2010;16:922–30.
58. Schneierson SJ. Continuous peritoneal irrigation in the treatment of intractable edema of cardiac origin. Am J Med Sci 1949;218:76–9.
59. Jaski BE, Ha J, Denys BG, Lamba S, Trupp RJ, Abraham WT. Peripherally inserted veno-venous ultrafiltration for rapid treatment of volume overloaded patients. J Card Fail 2003;9:227–31.
60. Ali SS, Olinger CC, Sobotka P. Enhanced sodium extraction with ultrafiltration compared to intravenous diuretics. Paper presented Heart Failure Society of America 2006 Scientific Meeting; September 11, 2006; Seattle, WA.
61. 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.
62. 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;96:191–9.
63. Marenzi G, Lauri G, Grazi M, Assanelli E, Campodonico J, Agostoni P. Circulatory response to fluid overload removal by extracorporeal ultrafiltration in refractory congestive heart failure. J Am Coll Cardiol 2001;38:963–8.
64. Pepi M, Marenzi GC, Agostoni PG, et al. Sustained cardiac diastolic changes elicited by ultrafiltration in patients with moderate congestive heart failure: pathophysiological correlates. Br Heart J 1993;70: 135–40.
65. Agostoni PG, Marenzi GC, Sganzerla P, et al. Lung-heart interaction as a substrate for the improvement in exercise capacity after body fluid volume depletion in moderate congestive heart failure. Am J Cardiol 1995;76:793–8.
66. 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;46:2047–51.
67. Mather PJ, Konstam MA. Newer mechanical devices in the management of acute heart failure. Heart Fail Rev 2007;12:167–72.
68. 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;46:2043–6.
69. Schroeder KL, Sallustio JE, Ross EA. Continuous haematocrit monitoring during intradialytic hypotension: precipitous decline in plasma refill rates. Nephrol Dial Transplant 2004;19:652–6.
70. Bradley SM, Levy WC, Veenstra DL. Cost-consequences of ultrafiltration for acute heart failure: a decision model analysis. Circ Cardiovasc Qual Outcomes 2009;2:566–73.
71. Kazory A, Bellamy FB, Ross EA. Ultrafiltration for acute decompensated heart failure: financial implications. Int J Cardiol 2012;154: 246–9.

Key Words: heart failure ■ loop diuretics ■ ultrafiltration ■ volume retention.