Fluid removal in acute heart failure: diuretics versus devices

Arun Krishnamoorthy[a,b] *and G. Michael Felker*[a,b]

Purpose of review
Fluid removal and relief of congestion are central to treatment of acute heart failure. Diuretics have been the decongestive mainstay but their known limitations have led to the exploration of alternative strategies. This review compares diuretics with ultrafiltration and examines the recent evidence evaluating their use.

Recent findings
Relevant recent studies are the Diuretic Optimization Strategies Evaluation trial (of diuretics) and the Cardiorenal Rescue Study in Acute Decompensated Heart Failure (of ultrafiltration). The Diuretic Optimization Strategies Evaluation study evaluated strategies of loop diuretic use during acute heart failure (continuous infusion versus intermittent bolus and high dose versus low dose). After 72 h, there was no significant difference with either comparison for the coprimary end points. Patients treated with a high-dose strategy tended to have greater diuresis and more decongestion compared with low-dose therapy, at the cost of transient changes in renal function. The Cardiorenal Rescue Study in Acute Decompensated Heart Failure study showed that in acute heart failure patients with persistent congestion and worsening renal function, ultrafiltration, as compared with a medical therapy, was associated with similar weight loss but greater increase in serum creatinine and more adverse events.

Summary
Decongestion remains a major challenge in acute heart failure. Although recent studies provide useful data to guide practice, the relatively poor outcomes point to the continued need to identify better strategies for safe and effective decongestion.

Keywords
acute heart failure, diuretics, fluid removal, ultrafiltration

INTRODUCTION

Heart failure remains a major public health concern worldwide [1]. In the United States alone, over five million individuals are currently estimated to have the syndrome, with a projected increase in prevalence by 25% by 2030 [2]. Heart failure is associated with both an increased mortality and a high burden of cost for the associated care [3▪▪]. New onset or worsening of heart failure symptoms that requires hospitalization (acute heart failure, AHF) is the most the common cause for hospitalization in patients over the age of 65 [3▪▪,4].

The signs and symptoms of AHF (dyspnea, orthopnea, edema, etc.) are primarily driven by hemodynamic congestion [5]. Various processes, including (but not limited to) myocardial ischemia, arrhythmias, hypertension, worsening renal function, and/or medical or dietary noncompliance, can precipitate and worsen hemodynamic congestion [6,7]. Successful treatment of patients with AHF consists of addressing the precipitants of decompensation, as well as safely and rapidly treating congestion while minimizing side-effects of therapy. Importantly, residual hemodynamic congestion (elevated ventricular filling pressures) can persist even after symptoms have improved [8].

Therapies for congestion have primarily centered on the use of diuretics, in particular the loop diuretics. These medications have been the mainstay treatment for congestion in AHF based primarily on observational data, but not without concerns over their efficacy and safety. As a result, alternative

[a]Division of Cardiology, Department of Medicine and [b]Duke Clinical Research Institute, Duke University School of Medicine, Durham, North Carolina, USA

Correspondence to G. Michael Felker, MD, Duke Clinical Research Institute, 2400 Pratt Street, Room 0311, Terrace Level, Durham, NC 27705, USA. Tel: +1 919 668 8919; fax: +1 919 668 7103; e-mail: michael.felker@duke.edu

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KEY POINTS

- Aggressive diuretic-based strategies for decongestion are relatively safe in AHF.
- Ultrafiltration in patients with AHF and worsening renal function (type 1 cardiorenal syndrome) was inferior to diuretic therapy for decongestion.
- As compared with ultrafiltration, diuretics remain the best initial strategy for fluid removal and decongestion in AHF.
- Further study is required to examine ultrafiltration in less sick patients and the relationship between diuretics, congestion, and worsening renal function.

strategies have emerged. Extracorporeal devices that are capable of performing ultrafiltration have several theoretical advantages over diuretic-based strategies, including the removal of isotonic volume (sodium as well as free water) and the potential for diuretic sparing. In this review, we will compare available data on diuretics versus ultrafiltration for the treatment of congestion and fluid removal in AHF.

DIURETICS

Several diuretic classes are used in the treatment of heart failure and consist of thiazide and thiazide-like diuretics, potassium-sparing agents such as mineralocorticoid antagonists, and loop diuretics. There is limited evidence defining the use of thiazides in combination with loop diuretics as a means to provide synergistic 'sequential nephron blockade'; this subject has recently been reviewed [9]. Loop diuretics, administered intravenously (i.v.), represent the primary diuretic strategy in AHF, and these agents will be the focus of this review.

Pharmacology

The loop diuretics act on the Na-K-Cl symporter in the thick ascending limb of the loop of Henle, thereby inhibiting sodium and chloride reabsorption and inducing production of hypotonic urine [10]. The commonly available loop diuretics are furosemide, torsemide, and bumetanide; the oral formulations of torsemide and bumetanide are more reliably bioavailable than oral furosemide and perhaps are therefore potentially preferred in certain situations [11]. Effects of an i.v. dose of furosemide are observed within 30 min of administration, with a peak after 1–1.5 h, and can last up to 6 h.

Efficacy, safety, and limitations

Recommendations for loop diuretic use in AHF stem mainly from expert opinion and, until recently, only limited retrospective evidence has been available to guide management [3▪▪,12]. Moreover, despite the widespread use of loop diuretics, concerns have arisen over the ability of these drugs to effectively decongest as well as potential negative sequelae associated with their use.

In over 90% of patients hospitalized with AHF, i.v. loop diuretics are prescribed [5]. However, recent work suggests that, despite use of these drugs, congestion often continues to remain as a symptom by time of discharge. For example, early relief of dyspnea (a symptom with multifactorial causes in AHF, but substantially related to pulmonary congestion) has generally been limited in the control groups of recent large randomized trials, even after rigorous attempts at decongestion with diuretic-based strategies [13,14,15▪].

Loop diuretics at high doses may also have deleterious effects, including further neurohormonal activation (and perpetuation of the vicious cycle of heart failure pathophysiology), electrolyte abnormalities, and worsening renal function. In turn, worsening renal function during AHF, also known as type 1 cardiorenal syndrome, has been associated with worse outcomes such as rehospitalization and mortality [16▪,17]. Similarly, worse outcomes have been associated with high-dose loop diuretic, even after attempts at statistical adjustment for other confounders [18]. These later associations with diuretics, however, have been potentially confounded, as higher doses of loop diuretics are often used in more severely ill heart failure patients. Thus, aggressive use of loop diuretics may simply highlight the severity of underlying disease, as opposed to mediating these negative consequences.

Moreover, patients may develop resistance to diuretic use and inability to decongest despite treatment with high doses. At the level of the renal tubule, diuretic resistance results from both acute and chronic processes [11]. After loop diuretic administration and waning of effect, a 'braking' phenomenon occurs in which the kidneys attempt to mitigate the recent diuretic-induced intravascular depletion by preventing further volume losses. Until the subsequent dose of loop diuretic is administered, sodium is thus avidly reabsorbed (potentially, this rebound phenomenon could be avoided by continuous, as opposed to bolus i.v., diuretic dosing) [12]. Chronic administration of loop diuretics can also lead to hypertrophy of the distal tubule and increased sodium reabsorption, again potentially negating the benefits of loop diuretics. Finally, both intrinsic renal disease (a common comorbidity in

heart failure) and type 1 cardiorenal syndrome can contribute to diuretic resistance [11,16▪,17]. A reduction in the glomerular filtration rate from these processes leads to decreased delivery of diuretic to the renal tubules; thus the ability of the drug to inhibit sodium and chloride reabsorption at this level is reduced.

Diuretic strategies in acute decompensated heart failure

In light of the uncertainty about the best strategy for giving loop diuretics during AHF, the prospective, randomized clinical trial Diuretic Optimization Strategies Evaluation (DOSE) was undertaken [12,19]. In a group of 308 patients with AHF, the use of bolus versus continuous dosing of furosemide and low-dose versus high-dose regimens was studied in a 2×2 factorial design over a 72-h period. Patients received furosemide by either an i.v. bolus every 12 h or a continuous infusion. The dose of loop diuretic was either a total i.v. dose equivalent to the patient's total daily home oral loop diuretic dose (low-dose strategy) or a total i.v. dose 2.5 times the total daily home oral loop diuretic dose (high-dose strategy). The coprimary end points were patient global assessment of symptoms, measured with the use of a visual-analog scale and quantified as area under the curve (AUC) of serial assessments from baseline to 72 h and change in serum creatinine from baseline to 72 h.

In the comparison of bolus with continuous infusion, there was no significant difference between route of administration in either global assessment of symptoms ($P = 0.47$) or the mean change in the creatinine level ($P = 0.45$). In the high-dose strategy as compared with the low-dose strategy, there was a nonsignificant trend toward greater improvement in global assessment of symptoms in the high-dose group (mean AUC, 4430 ± 1401 versus 4171 ± 1436; $P = 0.06$). The high-dose strategy was associated with greater diuresis and weight loss, but also with transient worsening renal function ($+0.08 \pm 0.3$ versus $+0.04 \pm 0.3$ mg/dl; $P = 0.21$). However, despite transient worsening renal function, there was no significant difference between the high-dose and low-dose groups in a 60-day composite of death, readmission, or emergency department visits between the different diuretic dose groups (hazard ratio 0.83, 95% confidence interval 0.60–1.16; $P = 0.28$). The results of the primary end points of DOSE are summarized in Table 1. In sum, the DOSE study did not find a difference between bolus and continuous i.v. loop diuretic administration. In addition, in the comparison of high versus low dose, the comparable safety of high-dose diuretics provides some reassurance for aggressive decongestion strategies. Higher-dose diuretics were observed to be associated with increased decongestion, and changes in renal function were modest, transient, and not associated with worsened long-term outcomes. These findings also potentially help to support other work, suggesting that the main hemodynamic driver of worsening renal function is congestion and that, in turn, decongestion may improve renal function and outcomes [20,21]. In general, the results of DOSE support the practice of aggressive attempts at decongestion even at the possible expense of transient changes in renal function.

DEVICES

The use of extracorporeal devices to remove fluid has been offered as an alternative strategy to diuretics in order to improve symptoms of congestion. Development of bedside devices for fluid removal, or ultrafiltration, has led to renewed interest in this approach, although the concept dates back many years [22].

Mechanisms

Ultrafiltration functions by removing isotonic plasma water across a semipermeable membrane with the assistance of a transmembrane pressure gradient. Importantly, solutes cross the membrane freely to create this isotonic fluid. A potential advantage with ultrafiltration involves the more

Table 1. Primary end points at 72 h for each treatment comparison in Diuretic Optimization Strategies Evaluation

End point	Bolus every 12 h ($N = 156$)	Continuous infusion ($N = 152$)	*P*-value	Low dose ($N = 151$)	High dose ($N = 157$)	*P*-value
Global assessment of symptoms (AUC)	4236 ± 1440	4373 ± 1404	0.47	4171 ± 1436	4430 ± 1401	0.06
Mean change in serum creatinine (mg/dl)	+0.05	+0.07	0.45	+0.04	+0.08	0.21

AUC, area under the curve.

effective removal of total body sodium, as persistent retention of sodium obligates passive retention of water, and possibly perpetuation of congestion [23]. Similarly, hypokalemia and hypomagnesemia can also be potentially mitigated.

Ultrafiltration can be performed through a peripheral i.v. line at the bedside via a venovenous connection. Fluid can be removed at rates as high as 500 ml/h, but the rate can be adjusted and optimized for steady removal. Rates of removal are commonly around 250 ml/h. As fluid is removed from the intravascular space, interstitial fluid is mobilized to replace these losses. Theoretically, removal of fluid from the intravascular space can be titrated to match the movement of fluid from the interstitial space into the vasculature, thus avoiding transient intravascular volume depletion that may lead to renin-angiotensin-aldosterone system activation. Optimization of plasma refill can be monitored by clinical parameters and lab values such as serial hematocrits [24].

Prior outcomes

The RAPID-CHF (Relief for Acutely Fluid-Overloaded Patients with Decompensated Congestive Heart Failure) and UNLOAD (Ultrafiltration versus Intravenous Diuretics for Patients Hospitalized with Acute Decompensated Heart Failure) trials were some of the initial studies to evaluate the technique of ultrafiltration in AHF. As compared with diuretics, the 20 patients in RAPID-CHF treated with ultrafiltration showed improvements in fluid removal after 24 h and in dyspnea and heart failure symptoms at 48 h [25]. The UNLOAD trial examined ultrafiltration versus diuretics as an initial strategy for decongestion [26]. Two hundred patients treated with ultrafiltration had greater weight loss, but not improvements in dyspnea at 48 h (the primary end points). Importantly, a significant reduction in heart failure hospitalizations was reported with ultrafiltration, although the total number of events was small. These studies were preliminary and, as such, ultrafiltration may be considered as an American Heart Association Class IIb recommendation, to be used for obvious volume overload or as a salvage therapy with failure of medical treatment [3▪▪].

Cardiorenal Rescue Study in Acute Decompensated Heart Failure

The Cardiorenal Rescue Study in Acute Decompensated Heart Failure (CARRESS-HF) trial was undertaken to further examine the safety and efficacy of ultrafiltration, specifically its use as a 'rescue therapy' in a population of AHF patients with worsening renal function and persistent congestion. Patients were randomized to either a diuretic-based stepped pharmacologic therapy or venovenous ultrafiltration [27,28]. Overall, 108 patients were enrolled; in the patients treated with i.v. diuretics, a goal urine output of 3–5 l/day was set, whereas in the patients treated with ultrafiltration the removal rate was set at 200 ml/h. The primary end point was the change in the serum creatinine level and the change in weight, considered as a bivariate response, 96 h after randomization. Secondary end points included the rate of clinical decongestion (defined as jugular venous pressure of less than 8 cm of water, no more than trace peripheral edema, and the absence of orthopnea) and measures of global well-being and dyspnea.

The results showed that ultrafiltration was inferior to pharmacologic therapy with respect to the bivariate end point of the change in the serum creatinine level and body weight 96 h after enrollment ($P = 0.003$), primarily as a result of an increase in the creatinine level in the ultrafiltration group. There was no significant difference in weight loss after 96 h between patients in the pharmacologic therapy group and those in the ultrafiltration group ($P = 0.58$). Additionally, a higher percentage of patients in the ultrafiltration group than in the pharmacologic therapy group had a serious adverse event, such as renal failure and complications related to bleeding or other complications related to vascular access (72% versus 57%, $P = 0.03$). The primary results of CARRESS-HF are highlighted in Table 2. With regard to secondary end points, there were no significant differences between the two groups, and overall the rate of clinical decongestion at 96 h was poor with either therapy (9% with pharmacologic therapy and 10% with ultrafiltration, $P = 0.83$).

Potential criticism of the CARRESS-HF design include the lack of adjustment of ultrafiltration rates and the lack of measurements of plasma refill rates, as well as the advanced population selected [29].

Table 2. Primary end points at 96 h in Cardiorenal Rescue Study in Acute Decompensated Heart Failure

End point	Ultrafiltration ($N = 92$)	Stepped pharmacologic therapy ($N = 94$)	*P*-value
Change in body weight (kg)	5.7 ± 3.9	5.5 ± 5.1	0.58
Mean change in serum creatinine (mg/dl)	$+0.23 \pm 0.70$	-0.04 ± 0.53	0.003

A more rigorous removal of fluid along with adjustment of rates might have led to improved decongestion; however, the rate of ultrafiltration was similar to prior studies. Alternatively, a slower and more prolonged duration of ultrafiltration might have led to better outcomes, but perhaps at the expense of less successful decongestion [30]. Of further interest is that the high doses of diuretics used in the control arm did not precipitate further renal deterioration. However, the relative ineffectiveness of either strategy to effectively clinically decongest patients by physical exam signs and clinical symptoms (less than 10% complete decongestion was achieved in either group) remains a concern.

FUTURE DIRECTIONS

With regard to ultrafiltration, it is clear that a better understanding of initial strategies to approach decongestion is required. The Aquapheresis versus Intravenous Diuretics and Hospitalizations for Heart Failure trial (ClinicalTrials.gov number, NCT01474200) will evaluate whether ultrafiltration as compared with i.v. diuretics reduces hospitalizations for AHF before the onset of worsening renal function, as an initial strategy [31]. The choice of loop diuretic used to decongest may also hold some relevance, with the suggestion from both prospective and retrospective data that torsemide may be a more effective drug with regard to improvement in functional classification, mortality, and costs [32]. Larger prospective, randomized control trial data are necessary to evaluate these findings. Finally, the use of higher, natriuretic doses of mineralocorticoid receptor antagonists, as is used to treat ascites from cirrhosis, has been posited as an alternative means to overcome diuretic resistance [33].

CONCLUSION

The identification of decongestion strategies that are well tolerated and effective remains a major unmet need in AHF. Taken together, the results of recent studies such as DOSE and CARRESS-HF suggest that aggressive diuretic-based strategies are relatively safe when compared with alternatives such as low-dose diuretics or ultrafiltration. The overall low rates of successful decongestion across multiple studies suggest the need for further research.

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Conflicts of interest

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