

EDITORIAL COMMENT

The Challenge of Correcting Volume Overload in Hospitalized Patients With Decompensated Heart Failure*

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Large databases obtained in the past decade from registries and clinical trials have allowed a better characterization of the clinical profile of patients admitted to hospitals for decompensated heart failure (DHF) (1–3). This new information has clearly recognized fluid overload and pulmonary congestion as the main reasons for hospitalization in the great majority of these patients (1–4). The potential detrimental effects of cardiopulmonary congestion and elevated ventricular filling pressure have also been well described (5).

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These effects include further neurohormonal activation, subendocardial ischemia and cell death by necrosis or apoptosis secondary to increased wall stress and decreased coronary perfusion, worsening of mitral and tricuspid regurgitation due to chamber dilation and spherical remodeling of the ventricles, and impairment of ventricular systolic and diastolic functions (5). Furthermore, correction of volume overload has been shown to have a favorable effect on symptoms and a positive effect on length of stay, rate of rehospitalization, and long-term survival (6–8) and should therefore be an important therapeutic goal. At the same time, however, recent publications clearly indicate that this therapeutic goal is often not achieved, and patients with DHF are frequently discharged with persistent symptoms and with minimal or no weight loss or even weight gain during the hospital stay (1,7). What is the reason for failure to achieve therapeutic goals in many patients admitted with DHF? Is it lack of effective therapy or ineffective use of

existing therapy? The answer to this question is probably both.

Non-potassium-sparing diuretics, especially loop diuretics given intravenously, have been the mainstay of therapy for fluid overload. This therapy is used in the great majority of patients with DHF (1) and has recently been recommended as the first-line therapy by the 2007 practice guidelines of the Heart Failure Society of America (9). Although these drugs can achieve effective diuresis in the majority of patients, their use in patients with DHF may be limited because of adverse effects such as electrolyte abnormalities, neurohormonal stimulation, and worsening of renal function (10). In addition, refractoriness to diuretics is common in patients with DHF and, therefore, achieving effective diuresis often requires aggressive strategies, including the use of loop diuretics either in high doses or in combination with thiazide diuretics. These practices, however, have been reported to be associated with worsening renal function, prolongation of length of stay, and increased long-term morbidity and mortality (11,12). Continuous infusion of loop diuretics has been shown to have a superior natriuretic and diuretic effect compared to intermittent bolus injections (13), but this treatment has not been commonly used; it should be used more often by clinicians for correction of fluid overload in patients with DHF.

Vasoactive medications are often used to facilitate diuresis in patients admitted with volume overload, especially those who seem resistant to diuretics. Although the inodilators dobutamine and milrinone have a potent hemodynamic effect and can significantly augment cardiac output (14), their effect on renal hemodynamics, as well as on urine output, in patients with DHF has not been sufficiently investigated and is therefore not clear. In addition, the administration of these drugs in hospitalized patients with DHF has been shown, in a number of studies, to be associated with increased risk of long-term morbidity and mortality (15), and their use has therefore been recommended only in selected patients (9). Renal dose dopamine has been shown to improve cardiac output, increase renal blood flow, and augment urine output in a small number of symptomatic patients with heart failure (HF) (16). The administration of this drug, however, may be associated with tachycardia and arrhythmias, and its effects in patients with DHF have not been extensively investigated.

Intravenous vasodilators are often used for the treatment of DHF (1), and recent guidelines have supported their use in addition to diuretics for rapid improvement of hemodynamic parameters and congestive symptoms in the absence of symptomatic hypotension (9). These drugs can effectively and rapidly reduce left ventricular (LV) filling pressure by virtue of their systemic vasodilatory effect, but their effect on the kidney has not been sufficiently studied (17). The effect of nitroglycerin on urine output in patients with DHF has not been evaluated, and infusion of the drug into the renal artery resulted in no significant effect on renal blood flow

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(17). An early study using hemodynamically effective doses of sodium nitroprusside also showed a significant diuretic and natriuretic effect in a small group of patients with HF (18). These potential effects of the drug, however, have not been further explored. The effect of nesiritide, a B-type natriuretic peptide, has been studied more extensively than that of nitroglycerin and nitroprusside. Most studies, however, have been limited to small numbers of patients, and the results have been conflicting (19,20). A recent study using nesiritide in a larger number of patients with HF undergoing cardiac surgery has demonstrated a superior effect on urine output compared with placebo (21). Enhancement of diuretic effect in this trial, as well as in other studies (20), may suggest a relation between the degree of volume overload and the effect of the drug on urine output. More information, however, is needed to explore the effect of nesiritide on urine output in patients with DHF.

Extracorporeal ultrafiltration (UF) has also been used to correct hypervolemia in patients with HF (22). Recent studies in relatively small numbers of patients showed that early application of newly designed veno-venous UF was feasible and well tolerated in patients with DHF and allowed a significant removal of fluid (23,24). This treatment resulted in symptomatic and hemodynamic improvement, as well as improvement in neurohormonal profile (22–24). In this issue of the *Journal*, Costanzo et al. (25) report the results of the first large-scale randomized study (UNLOAD [Ultrafiltration Versus Intravenous Diuretics for Patients Hospitalized for Acute Decompensated Congestive Heart Failure]) designed to assess the efficacy and safety of UF for the treatment of patients with DHF. In this study, 200 patients hospitalized for DHF secondary to left ventricular systolic dysfunction were randomized to either early UF (within 24 h of hospitalization) or to intravenous diuretics. The study clearly showed the efficacy and safety of UF in correcting fluid overload in a patient population with a mean net fluid loss of 4.6 l at 48 h without a significant change in serum creatinine or blood pressure. The study also demonstrated the clinical benefit of aggressive fluid removal in this patient population. A superior fluid loss achieved with UF compared to intravenous diuretics at the dose used in the study (4.6 vs. 3.3 l, $p = 0.001$) had a lasting effect and reduced the rate of rehospitalizations and unscheduled visits for 3 months after discharge. These data suggest that a rapid correction of volume overload with a careful and frequent monitoring of volume status and renal function is both safe and effective in patients with DHF.

It is interesting to note that a larger net fluid loss demonstrated in the UNLOAD study with UF compared to diuretics did not have an impact on length of stay. This finding should provide an important lesson to both clinicians and investigators and suggests that length of hospital stay in patients with DHF is often determined by multiple factors, some of them unrelated to patient response to therapy. These factors include adjustment of HF therapy before discharge, performance of diagnostic and therapeutic

procedures (echocardiogram, myocardial perfusion studies, magnetic resonance imaging, cardiac catheterization, percutaneous or surgical coronary interventions, cardioversion, etc.), treatment of comorbidities, social issues related to placement of patients after discharge, and lack of well-defined criteria and protocols for hospital discharge.

Should UF replace intravenous diuretics as a first-line therapy for patients with hypervolemia admitted for DHF? Although there are potential theoretical advantages to removal of excess volume with UF compared to diuretics (25), the validity of such a concept needs to be proven in larger studies designed to compare efficacy, safety, and cost-effectiveness of a comparable net fluid loss with these 2 therapeutic modalities in patients with DHF due to both systolic and diastolic LV dysfunction. The results of the UNLOAD trial, however, clearly demonstrate a great potential for the use of UF in patients with DHF who are either resistant to diuretics or demonstrate unfavorable side effects. An early application of this technology in such patients should allow effective therapy, prevention of adverse events, and improvement of after-discharge outcome.

In summary, clinical congestion due to volume overload is the main cause of hospitalization for patients with HF and is an important therapeutic target. Recent information suggests failure to achieve effective and rapid correction of this condition in many patients hospitalized for DHF, which results in prolongation of hospital stay and thus significant effect on quality of life, increased cost of therapy, and unfavorable after-discharge outcome. The results of the UNLOAD study suggest that UF is a safe and effective therapeutic modality for correction of volume overload in hospitalized patients with DHF due to LV systolic dysfunction. The use of this therapy should be considered early in patients not responding to intravenous diuretics and vasoactive medications and in patients in whom such therapy is discontinued or reduced because of worsening renal function or other drug-induced complications. A structured therapeutic approach to correction of fluid overload, including diuretics, vasoactive medications, and UF, should assure a rapid correction of LV filling pressure and cardiopulmonary congestion, and thus early improvement of symptoms, shortening of length of stay, and reduction in the need for rehospitalizations in this patient population.

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