



Introduction

Heart failure (HF) is an increasingly important source of morbidity and mortality in the United States and Europe. Although advances in the understanding and treatment of chronic HF have improved survival, the postdischarge prognosis of patients hospitalized with acute heart failure syndromes (AHFS) remains poor. The main reason for hospitalization for AHFS is related to worsening congestion rather than to low cardiac output, yet the most effective and safe approach to relieve the pulmonary and systemic congestion in AHFS remains to be established and will probably depend on the patient's blood pressure (high, normal, or low) at the time of presentation. Hemodynamic congestion (elevated left ventricular filling pressures) without clinical congestion (e.g., dyspnea, edema) often develops days to weeks before hospitalization for worsening HF. During hospitalization for AHFS, patients are often exposed to acute treatments (e.g., high doses of non-potassium-sparing diuretics or inotropes) that may have a short-term beneficial effect (symptom improvement), but these treatments may also have a negative effect on postdischarge outcomes (mortality and/or hospitalizations), which may be related to their effects on renal function (cardiorenal syndrome) and/or on viable but noncontractile myocardium (resulting in injury). Both renal dysfunction and myocardial injury may contribute to HF progression. Although congestion is the main cause for AHFS hospitalizations, a significant number of patients are nevertheless discharged with hemodynamic, if not clinical, congestion. Both hemodynamic and clinical congestion are associated with higher rates of postdischarge rehospitalization and death.

Effective strategies are needed not only to treat but also to assess congestion in patients hospitalized with AHFS. This approach hinges on the availability of therapeutic modalities and assessment tools for congestion. Direct measurement of pulmonary capillary wedge pressure via catheterization is the "gold standard" to evaluate hemodynamic congestion, but its invasive nature limits clinical utility. Although noninvasive modalities such as orthostatic blood pressure changes, jugular venous distention, imaging (chest

x-ray), and natriuretic peptide levels may aid the assessment of congestion, they also have limitations and are often underused.

This supplement to *The American Journal of Medicine* addresses the importance of congestion as a therapeutic target in AHFS and its pathophysiology. It also reviews the available or experimental therapies for congestion in HF and their limitations.

In the first article, Dr. Gerasimos Filippatos, Dr. Leonardo De Luca, Dr. John Burnett, and I review the epidemiology of AHFS, as well as the pathophysiology, evaluation, and management of pulmonary and systemic congestion. The significant role played by cardiac dysfunction, renal impairment, and neurohormonal activation in the pathophysiology of congestion in HF is discussed.

In the second article, Dr. Horng H. Chen and Dr. Robert W. Schrier review multiple pathophysiologic mechanisms that contribute to derangement in volume regulation. In HF, a further neurohormonal activation of the renin-angiotensin-aldosterone system, arginine vasopressin, and the sympathetic nervous system may occur in an effort to relieve renal sodium and water retention with non-potassium-sparing diuretics. Unfortunately, this neurohormonal activation may contribute to an increase in long-term mortality.

Complicating the overall management of HF for many patients is the presence of renal insufficiency. Atherosclerosis, diabetes mellitus, and hypertension are all recognized precursors of both HF and renal disease. In fact, >50% of patients hospitalized with AHFS have stage III or greater renal dysfunction as defined by the National Kidney Foundation (NKF). The renal insufficiency in HF has important implications in terms of management and prognosis. These renal abnormalities can be further aggravated by the use of high doses of non-potassium-sparing diuretics, causing a vasomotor nephropathy (cardiorenal syndrome) that is manifested by a significant increase in blood urea nitrogen (BUN) but not creatinine in the presence of continuing congestion (edema). Increase in BUN is one of the most important predictors of mortality risk in HF. Treatment strategies to address congestion and hemodynamic derangements in HF can impact renal perfusion and contribute to further renal deterioration. In the third article, Dr. Gregg C. Fonarow and Dr. J. Thomas Heywood review management strategies in patients with HF who have renal insufficiency

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and discuss the need to carefully balance congestion relief with the risk for exacerbating renal dysfunction.

In the fourth article, Dr. John G. F. Cleland, Alison Coletta, and Dr. Klaus Witte provide a comprehensive review of intravenous (IV) diuretic use in decompensated HF. Although diuretic therapy has been established as the standard approach to treating congestion in HF, few data from randomized clinical trials exist to support their use, and diuretic regimens vary. Long-term diuretics can effectively manage congestion for many HF patients, but their injudicious use may lead to unwanted symptoms and deleterious clinical effects. For example, IV loop diuretics effectively relieve congestion in AHFS, but they may lead to hypotension, as well as electrolyte abnormalities, worsening renal function, intravascular volume depletion, and neurohormonal activation. Moreover, many patients with advanced HF develop resistance to standard doses of IV loop diuretics and require progressively higher doses to relieve congestion. Retrospective analyses have reported that the use of high-dose diuretics may be associated with an increase in morbidity and mortality risk; these patients therefore may require alternatives to diuretic therapy in an effort to manage congestion. Randomized, controlled clinical trials of diuretic use in HF are needed to better characterize the most appropriate diuretic regimens that provide the greatest amount of benefit while minimizing risk.

In the final article, Dr. James A. Hill, Dr. Clyde W. Yancy, and Dr. William T. Abraham review pharmacologic

and nonpharmacologic strategies that currently exist to complement or replace diuretic therapy, especially in patients with advanced HF who exhibit diuretic resistance. Positive inotropes, IV nitrovasodilators, and natriuretic peptides all have been used to support hemodynamics and volume status in HF, but we lack the data from well-designed, randomized clinical trials that would allow us to routinely suggest a standard pharmacologic alternative or adjunct to diuretic therapy. However, the role of vasopressin antagonists such as tolvaptan is currently under investigation. The authors also discuss ultrafiltration as a nonpharmacologic alternative in AHFS in patients with resistance to diuretic therapy.

Effective and safe long-term management of congestion in HF is possible but often challenging because of the lack of consistent, randomized clinical trials and the consequent dearth of evidence-based guidelines to support a standard treatment regimen. With the increasing appreciation of the importance of congestion as a key target for therapy in HF, this supplement provides a critical evaluation of the benefits and drawbacks of available volume management strategies that will assist healthcare providers in coping with this challenging public health problem.

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