MAYO CLINIC

REVIEW

Volume Overload in Heart Failure: An Evidence-Based Review of Strategies for Treatment and Prevention

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Abstract

Acute decompensated heart failure is the leading cause of hospital admission in the United States, with a high risk of readmission within 30 days. Most acute decompensated heart failure admissions are driven by congestive signs and symptoms resulting from fluid and sodium overload. We reviewed the evidence base addressing the management and prevention of fluid overload in heart failure, focusing on recent clinical trials. All the references in this review were obtained through PubMed and had at least 1 of the following key words: *heart failure and volume overload, congestion, loop diuretics, thiazide diuretics, aldosterone antagonists, dopamine, cardiorenal syndrome, nesiritide, vasopressin antagonists, ultrafiltration, sodium restriction, fluid restriction, telemonitoring*, and *invasive hemodynamic monitoring*. We also reviewed relevant references cited in the obtained articles, especially articles addressing methods of treating or preventing volume overload in patients with heart failure.

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In the United States, 5.1 million Americans have heart failure (HF), and that number is expected to increase 46% by 2030.[1] Although treatments have improved, acute decompensated HF (ADHF) remains the leading cause of hospitalization, has a 50% 5-year mortality rate, and is costly, accounting for $30.7 billion in health care expenditures in 2012.[1] Heart failure occurs when cardiac output is insufficient to provide adequate blood flow to meet metabolic and circulatory demands. As a result, neurohormonal pathways are up-regulated, including the sympathetic nervous system, renin-angiotensin-aldosterone system, and vasopressin (or antidiuretic hormone) axis. Temporarily, mean arterial pressure and cardiac output increase to levels adequate for tissue perfusion; however, chronic neurohormonal activation is eventually deleterious, leading to salt and water retention and subsequent worsening of cardiac output.[2,3] Ultimately, excessive activation manifests with the familiar signs and symptoms of volume overload—the leading cause of ADHF hospitalizations.

In this review, we focus on treatments to remove excess fluid and prevent its accumulation in patients with HF, emphasizing recent clinical trials. All the references cited in this review have been obtained through PubMed using the following key words: *heart failure and volume overload, congestion, loop diuretics, thiazide diuretics, aldosterone antagonists, dopamine, cardiorenal syndrome, nesiritide, vasopressin antagonists, ultrafiltration, sodium restriction, fluid restriction, telemonitoring*, and *invasive hemodynamic monitoring*. We also reviewed relevant references cited in the obtained articles, especially articles addressing methods of treating or preventing volume overload in patients with HF.

STRATEGIES FOR FLUID REMOVAL

Diuretic Therapy

Diuretics are the mainstay of therapy in patients with congestive HF. Loop diuretics, which inhibit the Na-K-2Cl transport symporter, leading to decreased sodium absorption in the thick ascending loop of Henle, are most commonly used. If loop diuretics are not sufficient, additional synergistic diuretics that affect either the NaCl cotransporter (thiazides) or the renal mineralocorticoid receptor (aldosterone antagonists) are used.[4]

ARTICLE HIGHLIGHTS

- Although larger trials are needed, small studies suggest the superiority of torsemide compared with other available loop diuretics.
- Routine continuous intravenous infusion of loop diuretics offers no added benefits in removing fluid compared with intravenous bolus administration.
- Nesiritide and dopamine have limited, if any, roles in managing volume overload in patients with acute decompensated heart failure.
- Vasopressin antagonists may help decrease volume overload in patients with acute decompensated heart failure and hyponatremia.
- Ultrafiltration can remove fluid in diuretic-refractory patients, but clinical studies show no benefits compared with more intensive, optimal diuretic therapy regimens.
- Small observational and clinical studies have not shown a benefit in restricting sodium intake in patients with heart failure; further studies are required before a definitive conclusion can be reached.
- Implantable hemodynamic monitoring devices have a promising future, and their role in managing heart failure will continue to evolve in the next 5 to 10 years.

Loop Diuretics. Loop diuretics, which include furosemide, bumetanide, torsemide, and ethacrynic acid, are all generic. In the United States, furosemide was introduced much earlier than bumetanide and torsemide and is most commonly used. As a result, 87% of inpatients with ADHF are treated with furosemide, 3% with bumetanide, 0.4% with torsemide, and 10% with a combination of synergistic diuretics.[5]

Comparatively, loop diuretics are structurally similar, except for ethacrynic acid, which lacks a sulfa moiety. However, it is associated with a greater risk of ototoxicity, relegating its use to patients with allergies to sulfa-containing medications.[6,7] The other loop diuretics do have important differences in their pharmacokinetics (Table 1). For furosemide, the bioavailability ranges from 10% to 90%, with absorption decreasing in patients with severe ADHF-associated gut edema.[8,9] In contrast, bumetanide and torsemide are less affected by intestinal wall edema, allowing for higher and more predictable bioavailability ranging from 80% to 100%.[8,10] Once in the blood, concentration kinetics also differ; furosemide and bumetanide have half-lives of 1 to 3 hours and a 6- to 8-hour duration of action, and torsemide has a longer half-life at 4 to 6 hours, with a 12- to 18-hour duration of action.[8,11]

Compared with other loop diuretics, torsemide intrinsically blocks sympathetic nervous system and aldosterone activity, which may lead to favorable cardiac remodeling and decreased kaliuresis.[12-15] In an open-label, randomized controlled trial, patients treated with torsemide were found to have decreased myocardial fibrosis on 8-month endomyocardial biopsy specimens.[16] Although intriguing, only a few clinical outcome studies have subsequently compared torsemide with other loop diuretics. In an open-label trial, 234 hospitalized patients with ADHF were randomized to receive either furosemide or torsemide and continued the same diuretic treatment for 1 year. Despite being a sicker group (ie, more previous admissions for ADHF), the torsemide group had lower ADHF readmission rates (17% vs 32%) and spent fewer days in the hospital (106 vs 296 total days). In addition, the torsemide group had less fatigue but had no change in dyspnea.[17] In the outpatient setting, torsemide was examined in the TORIC (Torasemide in

TABLE 1. Loop Diuretic Comparison[a]

Characteristic	Furosemide	Bumetanide	Torsemide
FDA approval year	1966	1983	1993
Bioavailability (%)[8-10]	10-90	80-100	80-100
Half-life (h)[8,11]	1-3	1-3	4-6
Duration of action (h)[8,11]	6-8	6-8	12-18
Typical oral doses	40-160 mg 1-2 times per day Maximum: 600 mg/d	0.5-4 mg 1-2 times per day Maximum: 10 mg/d	20-80 mg/d Maximum: 200 mg/d
Cost ($/mo)[b]	14-40	30-75	60-90

[a]FDA = Food and Drug Administration.
[b]Wholesale prices from http://www.uptodate.com. Accessed February 10, 2015.

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