Management of acute heart failure

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Summary

Heart failure presents a substantial dilemma in the United States and Europe with a high prevalence and a persistent rise in admissions for acute episodes despite recent advances in the field. Evidence-based pharmacologic therapy has been well established in chronic heart failure, but acute management of decompensated heart failure is largely empiric. More trials are emerging regarding such treatment options. Inpatient treatment focuses on improving congestive symptoms and hemodynamics, avoiding renal dysfunction, treating reversible causes/comorbidities, and initiating evidence-based therapy prior to discharge. Pharmacologic management of acute heart failure episodes are reviewed, including investigational therapies.

Key words: heart failure; pharmacologic managements

Introduction

The burden of heart failure has become evident in our continued efforts to improve management, in terms of reducing symptoms and hospitalizations while improving outcomes, survival, and comorbidities. This burden is also evident in the latest statisitics. Acute decompensated heart failure (ADHF) accounts for nearly one million hospitalizations annually, a number that has continued to rise over the past few decades and is expected to climb further [1]. Prevalence in the United States is estimated at five million with an incidence of 400 000 new cases per year, responsible for approximately 250 000 annual deaths [1]. It has become the leading principal diagnosis in hospitalized patients over 65 years of age [2]; in fact, the average age of a patient admitted with decompensated heart failure in the Acute Decompensated Heart Failure Registry (ADHERE) was 75 years [3]. In a recent review of the National Hospital Discharge Survey data from 1979 to 2004, not only did heart failure-related hospitalizations increase during this time period, more than 80% of hospitalizations were among patients of at least 65 years and were paid by Medicare/Medicaid [4]. The proportion of hospitalizations resulting in transfers to short- and long-term care facilities increased, while the proportion of patients discharged home decreased.

The estimated cost of heart failure in the United States in 2007 was $ 33.2 billion [1]. High readmission rates contribute to this expense. The aging population in developed countries along with improved survival after revascularization for acute myocardial infarction have both added to the growing incidence of heart failure [5, 6].

As only a few randomized controlled trials exist regarding management of ADHF, treatment remains empiric, based on improving congestive symptoms and volume status, while initiating evidence-based therapy to improve mortality and morbidity.

Clinical presentation

Hospitalized patients may present with acute onset heart failure or acutely decompensated episodes of chronic *systolic or diastolic* heart failure. It is important to identify reversible or precipitating factors regardless of the presenting clinical scenario; these factors include assessing for ischemia, tachyarrhythmias (such as atrial fibrillation or other supraventricular arrhythmias), acute or chronic anemia, excessive alcohol consumption, recreational drug use, hypertension, hypo- or hyperthyroidism, prescribed drugs (such as antiarrhythmics, calcium channel blockers, NSAIDs), and noncompliance [7].

Evaluating the patient's hemodynamic profile aids in determining management of these patients; this profile is based on the presence of congestion (or elevated filling pressures) and the status of perfusion as obtained from symptoms and physical examination [8]. A patient is either "wet" or "dry" as determined by the presence of congestive symptoms, such as orthopnea or paroxysmal nocturnal dyspnea, or signs of congestion, such as jugular venous distension, positive hepato-

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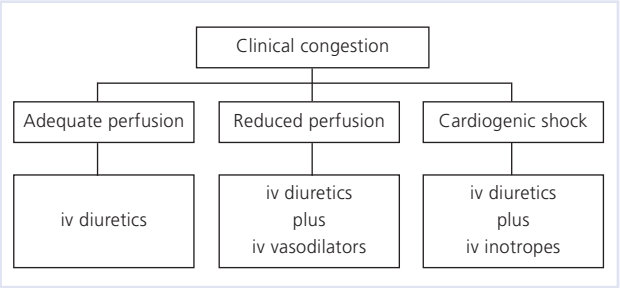
Figure 1
Profiles of presentation in the congested ("wet") patient with acutely decompensated heart failure and guide to therapy.



jugular reflex, peripheral edema or S_3. A patient is either "warm" or "cold" based on symptoms and signs of adequate or low perfusion (such as hypotension, tachycardia, cool extremities, or narrow pulse pressure).

We have found it useful to include a third category of perfusion termed "lukewarm", to describe the patient with reduced cardiac output but no impending cardiogenic shock (fig. 1). In general, patients who are "warm" have normal cardiac outputs (cardiac index >2.5 ml/min/m^2); patients who are "cold" have severe reductions in cardiac output (cardiac index <1.5 ml/min/m^2); and patients who are "lukewarm" fall in-between (cardiac index between 1.5 and 2.5 ml/min/m^2). While patients present to the hospital with varying degrees of perfusion, the vast majority (about 90%) are "wet" or congested [3].

This simple clinical assessment is applicable in daily practice and has been shown to predict prognosis and outcomes [9]. Additionally, this profile can be used to define the treatment approach. For example, in the "warm and wet" or "lukewarm and wet" patients, beta-blocker therapy will be maintained at chronic dosing but not initiated or up-titrated until the volume status has improved, while a "warm and dry" patient will tolerate further titration of this medication. A truly "cold" patient may require temporary down-titration or in extreme cases discontinuation of beta-blockade.

Most patients present with a "lukewarm and wet" hemodynamic profile (approximately 50–60%). These patients have reduced perfusion with evidence of volume overload; therefore, treatment is usually targeted at diuresis and lowering of filling pressures with vasodilators. They tolerate vasodilation with ACE inhibitors, angiotensin receptor blockade, or intravenous vasodilators, and often tolerate maintenance of their beta-blocker dose. However, the beta-blocker should be reduced by half (or held for a few days) in those who are not responding well to diuresis [7]. The next most common profile is the "cold and wet" patient, who would be considered in or near cardiogenic shock due to impaired end-organ perfusion with evidence of volume overload. These patients may require brief inotrope or vasopressor support, along with hemodynamic monitoring in high-risk patients, although the ESCAPE trial found no significant mortality benefit and no reduction in days hospitalized or days out of the hospital when using pulmonary artery catheters to guide medical therapy [10]. While the "warm and wet" profile is not uncommon, many of these patients are managed successfully out of the hospital. The "cold and dry" presentation is usually the least common presentation, demonstrating impaired end-organ perfusion without congestion; they may have a lower predisposition to congestion but become symptomatic with minimal exertion. Hydration should be attempted first, but these patients may require inotrope therapy due to their low cardiac reserve. The "warm and dry" patient has the best overall prognosis, as these are well-compensated patients with normal resting hemodynamics [7, 9].

Pathophysiology

Before reviewing the management of acute heart failure, it is imperative to review the pathophysiologic mechanisms behind the clinical syndrome. Hemodynamic abnormalities lead to elevated right and left sided filling pressures in heart failure, which, in turn, results in neurohormonal activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS) [11, 12]. Vasoconstriction results from angiotensin II, norepinephrine, endothelin, and vasopressin; vasoconstriction increases myocardial wall stress and reduces renal perfusion. Neurohormonal activation from aldosterone, antidiuretic hormone, and sympathetic stimulation also results in sodium and water retention, further exacerbating systemic and pulmonary congestion. The neurohormonal cascade also plays a role in the cardiorenal syndrome, resulting in dysfunction in either the heart or kidney leading to dysfunction of the other organ [11–13]. Increased immunomodulator levels (such as tumor necrosis factor, interleukin-6, and complement) mediate a proinflammatory response and myocardial apoptosis [14]; cardiac remodeling and fibrosis also develop from aldosterone effects. Pharmacologic therapy targets inhibition of the neurohormonal cascade responsible for this positive feedback loop.

Pharmacologic therapy

Diuretics

Diuretics have been a mainstay of treatment for hospitalized patients with ADHF, as seen in the ADHERE registry with loop diuretics the most commonly administered intravenous medication [15]. Although these drugs are widely accepted for symptomatic improvement, large randomized controlled trials have not evaluated outcomes with these drugs [12]. Loop diuretics inhibit Na-K-Cl transport in the ascending limb of the Loop of Henle, and thiazide diuretics inhibit transport in the distal convoluted tubule [16]. Thiazide

and potassium-sparing diuretics are typically less potent than loop diuretics.

Although hemodynamics generally improve with diuresis, these drugs result in RAAS and sympathetic stimulation, leading to further elevation in vasoconstricting substances, fluid retention, and worsening heart failure. Diuretic resistance is also a concern, with a decreased effectiveness noted with long-term therapy, advanced heart failure, and renal insufficiency. Exacerbating drugs (NSAIDs, nephrotoxic drugs), hypotension from shock or excessive vasodilation, hypovolemia, over-diuresis, and worsening renal function can all reduce diuretic responsiveness [7]. The "braking phenomenon" refers to the reduced natriuretic effect with chronic loop diuretic use, in which the distal renal tubule hypertrophies, and has an increased sodium resorptive ability [12]. For such patients, fluid and salt restriction (<2 gm and <2 L daily) should be initiated; combining a loop and thiazide diuretic may produce a synergistic effect. Also, a continuous infusion of lasix rather than high bolus doses has yielded better diuresis and sodium excretion in some studies [17, 18]. The potential adverse effects of diuretics are supported by data from the ADHERE registry; those treated with intravenous diuretics had a higher in-hospital mortality and longer length of stay compared to those who were not treated with intravenous diuretics, even after controlling for other factors [19].

Vasodilators

Intravenous vasodilator therapy includes nitroglycercin, nitroprusside, and nesiritide, which are recommended for treatment of decompensated heart failure in addition to diuretic therapy in patients who are not hypotensive and have failed outpatient management [20]. Nitroglycerin reduces preload but not afterload through stimulation of guanylyl cyclase and production of cGMP, producing relaxation of vascular smooth muscle through a series of steps that phosphorylate myosin light chains in the venous system [21]. Conversely, ni-

Table 1
Summary of the hemodynamic effects of pharmacologic therapies utilized in the management of acute decompensated heart failure.

Drug	Mechanism of Action	Inotropic Effect	Vasodilation	Vasoconstriction
Diuretics	Inhibit sodium and water retention	–	–	+ (through RAAS & SNS activation)
Nitroglycerin	↑ cGMP production in venous system	–	++ (venous: ↓ preload)	–
Nitroprusside	cGMP production in arterial, venous systems	–	++ (venous, arterial: ↓ preload & afterload)	–
Nesiritide	Activates cGMP	–	++ (venous, arterial: ↓ preload & afterload)	–
Dobutamine	↑ cAMP through β_1 agonist activity	++	+ (dose-dependent, β_2 effect)	±
Milrinone	↑ cAMP through PDEI activity	++	++	–
ACE inhibitors	RAAS inhibition of angiotensin I to angiotensin II	–	++ (venous, arterial)	–
ARB	Antagonism of angiotensin II receptor	–	++ (venous, arterial)	–
Hydralazine	Potent antioxidant, preserves NO levels	–	++ (arterial: ↓ afterload)	–
Vasopressin antagonists	Inhibit V_{1A} & V_2 receptors (water diuresis from V_2)	–	++ (V_{1A} inhibition, ↓ afterload)	–
Calcium sensitizer: Levosimendan	↑ calcium sensitivity of troponin C; K influx through ATP dependent channels	++ (Calcium affinity)	+ (↓ preload & afterload, K channels)	–

RAAS = Renin-angiotensin-aldosterone system; SNS = Sympathetic nervous system; cGMP = Cyclic guanosine 3′, 5′-monophosphate; cAMP = Cyclic adenosine 3′, 5′-monophosphate; PDEI = Phosphodiesterase enzyme inhibition; ACE = Angiogensin-converting enzyme inhibitors; ARB = Angiotensin receptor blockers; NO = Nitric oxide; ATP = Adenosine 5′-triphosphate; K = Potassium.

troprusside acts through another cGMP pathway affecting the smooth muscle in both the arterial and venous systems, reducing both preload and afterload. Both drugs are potent vasodilators. Table 1 summarizes the hemodynamic effects of vasodilators and other pharmacologic therapies currently used or emerging in the management of ADHF.

Nesiritide is recombinant human brain natriuretic peptide, and activates cGMP through guanylate cyclase. It has multiple effects, including arterial and venous vasodilation, coronary vasodilation, neurohormonal inhibition and reduction of cellular effects, and enhancement of diuretic effect. Nesiritide has been shown to significantly reduce filling pressures when compared to nitroglycerin [22] and was associated with a lower six month mortality when compared to in-hospital inotrope therapy [23]. A possible explanation could be the lower potential for nesiritide to promote ventricular arrhythmias compared to inotropes [24]. However, the issue of its effect on mortality is still controversial, as two different pooled meta-analyses of previous trials suggested a non-significant increase in 30 day mortality [25, 26]; these studies were not controlled for risk factors and had significant baseline differences among treatment and control groups [27]. More patients in the nesiritide groups were treated with dobutamine and Class III anti-arrhythmic agents than the control vasodilator groups. Recently, the ADHERE registry suggested a lower in-hospital mortality with intravenous vasodilator therapy compared to inotrope therapy [28]. Although there does not seem to be an increase in long-term mortality (3 and 6 months), controversy remains about in-hospital and 30 day outcomes, which will be addressed in the currently enrolling ASCEND-HF trial [29]. Current recommendations state nesiritide may be considered in the absence of hypotension, as an addition to diuretics for rapid improvement of congestive symptoms in ADHF for those who have failed aggressive treatment with diuretics and standard oral therapies [20].

Inotrope

Inotropes are used in the hypoperfused patient, or those with a "cold" profile. Dobutamine, a beta-1 and beta-2 receptor agonist, is most commonly used with an onset of action of 1–2 minutes, followed by milrinone, a phosphodiesterase-III inhibitor with a half-life of 30 to 60 minutes [21]. The mechanism of action behind both involves increased cAMP which raises intracellular calcium levels from the sarcoplasmic reticulum and myocardial contractility.

Although these drugs provide hemodynamic benefits with improved stroke volume and filling pressures, longterm mortality and increased cardiovascular events have been seen in studies, such as OPTIME-CHF and the Flolan International Randomized Survival Trial [30, 31]. Of note, in a post-hoc analysis of OPTIME-CHF, there was no difference in 60 day mortality between milrinone and placebo in non-ischemic patients, but a greater mortality in ischemic patients [32]. Currently, these drugs are recommended for symptomatic relief in refractory patients who require increased cardiac output (Stage D patients), as a bridge to transplantation or ventricular assist device, or as palliative treatment in end-stage patients. Milrinone should be used in patients who can tolerate its hypotensive effects with preload and afterload reduction; for this reason, a bolus is usually not given. Inotrope therapy should be titrated down as hemodynamics improve, while transitioning patients to an appropriate oral regimen.

Ultrafiltration

Sodium and fluid retention are well known features of decompensated heart failure, and, as previously mentioned, are exacerbated by neurohormonal activation and the interaction of worsening cardiac and renal dysfunction. Diuretics provide short-term relief of symptoms, but also contribute to this continuous cycle and ultimately impair glomerular filtration rate. Ultrafiltration involves mechanical volume removal across the filter through convective forces; it removes both water and electrolytes but is isotonic to plasma compared to the hypotonic filtrate achieved with diuretic therapy [33]. This reduces hydrostatic pressure and, subsequently, the likelihood of renin-angiotensin aldosterone activation, along with further neurohormonal inhibition and reduced levels of norepinephrine and cytokines.

Ultrafiltration requires venous access through a large bore, double lumen central catheter, or more recently, peripheral access [34]. It also consists of a console unit, 0.12 m^2 polysulphone filter circuit, physician choice in rate of fluid removal up to 500 ml/hr, and does not require a nephrologist. Small randomized studies have been promising with improved exercise capacity or time and reduced filling pressures [35, 36]. The UNLOAD trial (Ultrafiltration vs IV Diuretics for Patients Hospitalized for Acute Decompensated CHF) is the largest study to date enrolling 200 patients and found a significantly greater weight and fluid loss with ultrafiltration, along with a lower heart failure rehospitalization and unscheduled visit rate during 90 day follow-up [37]. Ultrafiltration appeared safe and effective, with no significant difference in serum creatinine when compared to diuretic therapy. Disadvantages to such therapy include poor peripheral access in many patients, requiring central lines, expense (approximately $ 25 000 for the device and $ 900 for supplies per usage), and simultaneous anticoagulation to prevent frequent clotting of the filtration system [33]. Ultrafiltration is recommended in inpatients with elevated filling pressures who exhibit diuretic resistance and have not responded to intravenous vasodilator therapy; it is

also beneficial when patients exhibit renal dysfunction with acute or chronic elevation in serum creatinine. Further long-term outcome data, including effect on mortality, is needed to aid in determining the role of ultrafiltration in acute decompensated heart failure.

Oral vasodilators: ACE inhibitors, angiotensin receptor blockers, hydralazine and nitrates

Inpatients with ADHF should be maintained on their outpatient vasodilator regimen if possible, unless they require IV vasodilator therapy or have evidence of impaired perfusion and hypotension preventing treatment with these drugs. While weaning IV vasodilator regimens in these patients, oral vasodilator therapy should be folded into the medical regimen. Ideally, drugs that provide both arterial and venous dilation, or reduction in both preload and afterload, should be initiated (ACE inhibitors, angiotensin receptor blockers), but the combination of hydralazine and nitrates can be used as a substitute in patients with significant renal dysfunction, creatinine >2.5 to 3 mg/dl, or in addition to standard therapy in African American patients with advanced heart failure, due to concerns that ACE inhibition is less effective in this subset of patients [38, 39].

Beta-blockers

The benefit of beta-blockers in heart failure has been well established; these drugs inhibit the negative effects of sympathetic stimulation in heart failure [40]. When patients are admitted with ADHF, a frequent question asked by practitioners is how to handle their chronic beta-blocker therapy. If a patient is only mildly overloaded and responds well to diuretic therapy, then the maintenace dose should be continued; the dose may be reduced in half in patients who are more symptomatic or do not respond well to diuresis [7]. However, if they are hemodynamically unstable or have poor perfusion, their beta-blocker will have to be held. These drugs should not be titrated up during acute episodes of decompensated heart failure, but should be initiated before discharge after an episode has stabilized.

Aldosterone antagonists

The benefit of aldosterone antagonism lies in the promotion of reverse remodeling of the left ventricle, not diuretic effects of these drugs. Randomized trials have shown antagonism-improved morbidity and mortality in advanced heart failure and in post-myocardial infarction heart failure [41, 42]. However, in ADHF patients who are naïve to this drug, therapy should be initiated after the acute episode has been treated prior to discharge. It should be continued in those who are on it chronically, unless there are electrolyte or renal issues [7].

Emerging therapies

Arginine vasopressin is produced by the central nervous system and results in vasoconstriction and water resorption. Newer drug therapy being developed for use in heart failure is based on vasopressin antagonism at the V_{1A} receptor, yielding vasodilation and reduced afterload, and antagonism at the V_2 receptor, producing water excretion [43]. This free water excretion improves hyponatremia without affecting serum potassium, could possibly reduce required diuretic doses, has not been shown to affect glomerular filtration rate, and ideally will improve patient outcomes. Thirst is the major side effect, and serum sodium should be monitored to ensure that it does not rise too rapidly, as osmotic demyelination is a concern. Conivaptan is a combined V_{1A} and V_2 receptor antagonist, whereas tolvaptan and lixivaptan are selective for V_2 (therefore, referred to as an "aquapheretic" drug). Safety and efficacy of tolvaptan has been evaluated in a trial of 319 ADHF inpatients with promising results; there was no in-hospital mortality difference or worsening heart failure in the follow-up period [44]. Tolvaptan-treated patients had a signficant reduction in weight in 24 hours and improvement in hyponatremia was maintained at 60 days. The EVEREST trial was an outcome trial in 4133 patients, and found no effect on long-term mortality or heart failure morbidity for patients treated with tolvaptan for acute heart failure management [45].

Calcium-sensitizing agents are newer drugs that augment calcium troponin C binding, allowing for enhanced interaction between actin and myosin filaments facilitating contractility without increasing the calcium concentration. In addition to this effect, levosimendan produces vasodilation by stimulating ATP-dependent potassium channels in vessels. Most studies have shown improved mortality rates relative to placebo and inotrope [46–49]. The Levosimendan Infusion vs Dobutamine trial found significantly improved hemodynamics (in terms of cardiac index and pulmonary capillary wedge pressure) and lower mortality (26 vs 38%, $p = 0.029$) with levosimendan in 203 patients, but no difference in symptomatic improvement [47]. This therapy is promising in acute episodes of heart failure, but more definitive data will establish its role in management.

Endothelin antagonists, such as bosentan and tezosentan, result in vasodilation due to inhibition of the potent vasoconstricting neurohormone, endothelin-1. Overall, studies with these drugs have not been satisfactory with no significant improvement noted in multiple studies [50–52].

Adenosine antagonists facilitate diuresis through inhibition of A1 receptors [53]. The PROTECT trial was a pilot study using rolofylline in ADHF without impairing renal function and also found a trend to improved 60 day mortality and reduced readmission rates for cardiac or renal causes. However, a larger patient

trial failed to demonstrate a benefit of this agent in ADHF [54]. Other adenosine receptor antagonists have shown promise in heart failure and remain under investigation [55, 56].

Finally, urodilatin – a natriuretic peptide produced within the kidneys – has shown great promise for the treatment of ADHF [57]. Based on its pharmacological profile, urodilatin may have advantages over other natriuretic peptides studied for the treatment of ADHF. Future studies of urodilatin should clarify its potential role in ADHF management.

Conclusion

Management of ADHF targets relief of congestive symptoms, often starting with diuretic use. It is important to assess a patient's hemodynamic profile in order to determine appropriate treatment; usually, this can be done quickly at the bedside without the use of invasive hemodynamic monitoring. Continuous infusion of diuretics or addition of a thiazide should be considered in order to improve patient response. Additionally, those with elevated filling pressures who do not have significant end-organ hypoperfusion should be aggressively vasodilated with nitroglycercin, nitroprusside, or nesiritide. Ultrafiltration is beneficial in diuretic-resistant patients and those with renal dysfunction. Inotropes should be used in hemodynamic compromise with impaired end-organ perfusion, with the goal of weaning this therapy due to the associated long-term adverse outcomes. Promising therapies include vasopressin, adenosine antagonists and urodilatin. Larger clinical trials are needed to provide further treatment options for ADHF.

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