Pharmacologic Therapies for Acutely Decompensated Heart Failure

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The management of acutely decompensated heart failure in the emergency medical setting poses a major clinical challenge. Acutely decompensated heart failure is characterized by hemodynamic abnormalities and neuroendocrine activation that contribute to heart failure symptoms, end-organ dysfunction, arrhythmias, and progressive cardiac failure. The therapeutic goals in patients presenting with acutely decompensated heart failure are to stabilize the patient, reverse acute hemodynamic abnormalities, rapidly reverse dyspnea and/or hypoxemia caused by pulmonary edema, and initiate treatments that will decrease disease progression and improve survival. Pharmacologic therapies to impact the hemodynamic abnormalities and symptoms in patients with acutely decompensated heart failure include diuretics, inotropic agents, vasodilators, and natriuretic peptides. In patients with acutely decompensated heart failure, it has recently been demonstrated that elevation in left ventricular filling pressure is the hemodynamic abnormality that most directly impacts heart failure symptoms and is highly predictive of increased risk of fatal decompensation and sudden death. Measures of systemic perfusion, arterial pressure, and vascular resistance have not been predictive of symptoms or clinical outcomes. An ideal agent for acute decompensated heart failure would be one that rapidly reduces pulmonary wedge pressure, results in balanced arterial and venous dilation, promotes natriuresis, lacks direct positive inotropic effects, and does not result in reflex neuroendocrine activation.

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Patients presenting to the emergency department (ED) with acutely decompensated heart failure (ADHF) pose a major health care problem.[1] These patients are often hemodynamically unstable and have disabling symptoms of dyspnea secondary to pulmonary edema. Rapid application of effective interventions is frequently required to achieve clinical stability and avoid the need for mechanical ventilation. After evaluation and stabilization in the ED, most patients will require hospital admission, although a subset of low-risk

patients may be appropriate for discharge home following a period of observation. The in-hospital mortality rate for ADHF is 5%–8%.[1,2] Patients with ADHF face a median 6-day duration of hospitalization and a rehospitalization rate over the next 6 months as high as 50%.[1,2] ED visits and subsequent hospitalizations for ADHF continue to constitute a major public health burden, with hospitalizations for heart failure having increased from 577,000 in 1985 to 970,000 in 1998 in the United States.[2] The major expenditure for heart failure care is on hospitalizations, with an estimated $23 billion spent on the inpatient management of ADHF.[2]

Advances in the understanding of the pathophysiology of ADHF and recent clinical trials have provided new insight into successful treatment strategies to reverse ADHF rapidly.[3] The therapeutic goals in patients presenting with ADHF are to reverse acute hemodynamic abnormalities, rapidly relieve symptoms, and initiate treatments that will decrease disease progression and improve survival. In the past, ADHF was often viewed as merely a disorder of volume overload and low cardiac output. Focus on acute maximization of cardiac output led to therapies that increased mortality.[3] Use of intravenous diuretics alone led to further increases in systemic vascular resistance and further deleterious neurohumoral activation.[4] More recently, it has become apparent that in most cases ADHF/pulmonary edema is related to a marked increase in systemic vascular resistance superimposed on insufficient systolic and diastolic myocardial functional reserve.[3,5,6] Therefore the emphasis in treating ADHF has shifted from diuretic monotherapy and/or intravenous inotropic agents to intravenous vasodilators.[5] This more physiologic approach to ADHF has been shown to relieve symptoms more rapidly and reduce patient morbidity, and thus has the potential to help control rising health care costs by reducing admissions, length of stay, and rehospitalization.

Focus on acute maximization of cardiac output led to therapies that increased mortality.

Hemodynamic Mechanisms in Acutely Decompensated Heart Failure

ADHF is characterized hemodynamically by elevated right and left ventricular filling pressures, decreased cardiac output, and increased systemic vascular resistance.[3,7] The initial response to decreased systolic performance is an increase in myocardial preload (ventricular filling pressures) and afterload (systemic vascular resistance), which serves to maintain systemic arterial pressures. Systolic performance is, however, not enhanced but is actually further compromised by the persistent increase in loading conditions, because atrioventricular valve regurgitation increases out of proportion to any total increase in stroke volume.[5] The sustained increases in cardiac volume and pressure lead to increased wall stress and myocardial oxygen demands which can adversely affect left ventricular performance and can set the stage for acute decompensation.[5] These hemodynamic alterations contribute to patients' symptoms, exercise intolerance, and clinical decompensation, which result in emergency medicine center visits and hospitalizations.[3,5]

The emphasis in treating ADHF has shifted from diuretic monotherapy and/or intravenous inotropic agents to intravenous vasodilators.

Until recently, the pathogenesis of ADHF leading to pulmonary edema was believed to result from fluid accumulation in the lungs because of systemic volume overload.[6] However, decompensation of heart failure and pulmonary edema may occur rapidly, developing over a few hours or even minutes. Therefore, net fluid accumulation cannot be the sole mechanism of pulmonary edema. More recent data instead indicate that a process of fluid redistribution takes place by which a portion of the intravascular volume is redistributed to the lungs.[5,6] Increases in systemic vascular resistance contribute to this rapid redistribution of fluid. In patients with ADHF due to systolic dysfunction, hemodynamic measurements revealing marked elevation in systemic vascular resistance accompany the elevations in pulmonary capillary wedge pressure (PCWP) and reduced cardiac index.[7,8]

The interaction between vascular resistance and myocardial systolic and diastolic reserve as a mechanism of pulmonary edema was studied by Gandhi and colleagues by measuring cardiac contractility in patients with pulmonary edema presenting to the ED.[6] They found that echocardiographic ejection fraction was almost within normal range (EF 0.50 ± 0.15). The most significant finding during

acute pulmonary edema was diastolic dysfunction and elevated systemic vascular resistance. Thus peripheral vasoconstriction plays a major role in the process of decompensation in systolic and isolated diastolic dysfunction heart failure. ADHF is caused by a combination of events in which inappropriate increase in vascular resistance is met with insufficient systolic and diastolic myocardial functional reserve, leading to acute afterload mismatch.[5] A vicious cycle is established in which impaired function is met with inappropriately high resistance, causing additional increases in atrioventricular valvular regurgitation and decreased forward stroke volume. This increased vascular resistance leads to increased left ventricular diastolic pressure which is transferred backwards to the pulmonary veins, leading to pulmonary edema.

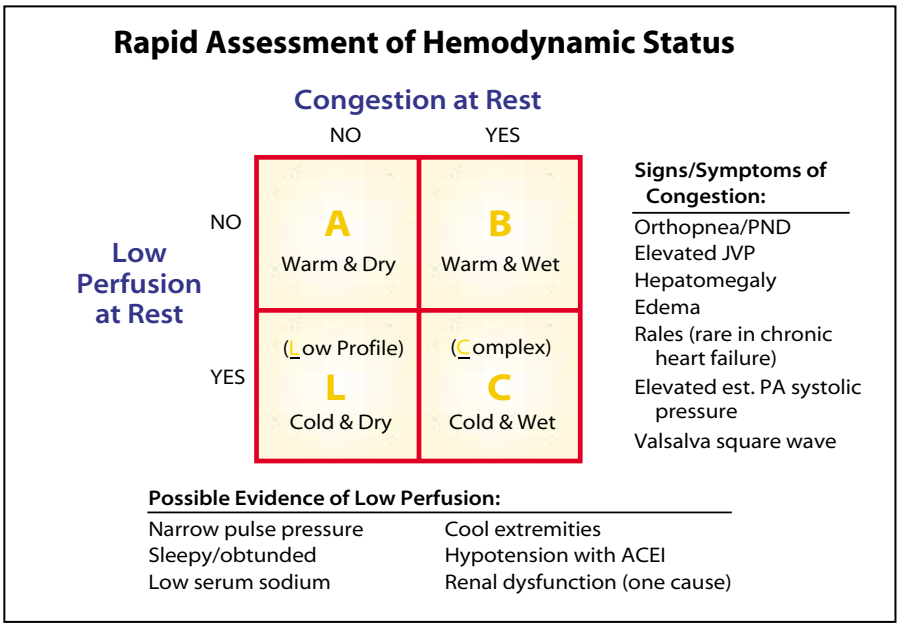

Figure 1. *Profiles and therapies of advanced heart failure. Clinical or hemodynamic assessment can be used to classify patients into four hemodynamic profiles. Patients hospitalized with acutely decompensated heart failure usually have congestion at rest. PND, paroxysmal nocturnal dyspnea; JVP, jugular venous pressure; PA, pulmonary artery; ACEI, angiotensin converting enzyme inhibitor.*

Hemodynamic Assessment

The rapid assessment of ADHF patients can be simplified by the consideration of four hemodynamic profiles.[3] Most ADHF patients can be classified into one of these four profiles during a 2-minute bedside assessment, as described by Stevenson and colleagues.[3] The two fundamental hemodynamic parameters relate to presence or absence of elevated filling pressures (wet or dry) and perfusion that is adequate or critically limited (warm or cold) (see Figure 1). In patients monitored with a pulmonary artery catheter, congestion corresponds to elevated PCWP and low perfusion corresponds to low cardiac index.

Over 90% of patients presenting with ADHF have clinical congestion (classified as being wet) and, if right heart catheterization were performed, would show elevated PCWP.[3] These patients may have adequate or reduced perfusion, with the majority showing elevation in systemic vascular resistance. Identification of congestion (elevated filling pressures) in acute decompensation of chronic heart failure relies heavily on the symptoms of dyspnea and orthopnea and the finding of elevated jugular venous pressure. Rales are absent in more than 80% of patients with chronically elevated filling pressures due to compensation of the pulmonary lymphatics.[3] Residual pulmonary interstitial fluid frequently causes marked distress from the sensation of restricted inspiration. Peripheral edema is relatively insensitive to elevated filling pressures in patients with heart failure or may be caused by noncardiac causes. A third heart sound may or may not be detected. The most assessable indicator of perfusion is blood pressure and pulse pressure.[3] The use of this hemodynamic classification system allows for more appropriate targeting of therapy in patients presenting with acutely decompensated heart failure.

Peripheral vasoconstriction plays a major role in the process of decompensation.

Treatment Goals in Acutely Decompensated Heart Failure

The majority of patients presenting with ADHF have congestion and reduced perfusion in the absence of cardiogenic shock. The traditional goals of acute heart failure therapy in these patients were to reduce extracellular fluid volume excess and improve hemodynamics by increasing cardiac output.[5] Hence, these patients have been traditionally treated with intravenous diuretics to reduce volume and/or intravenous

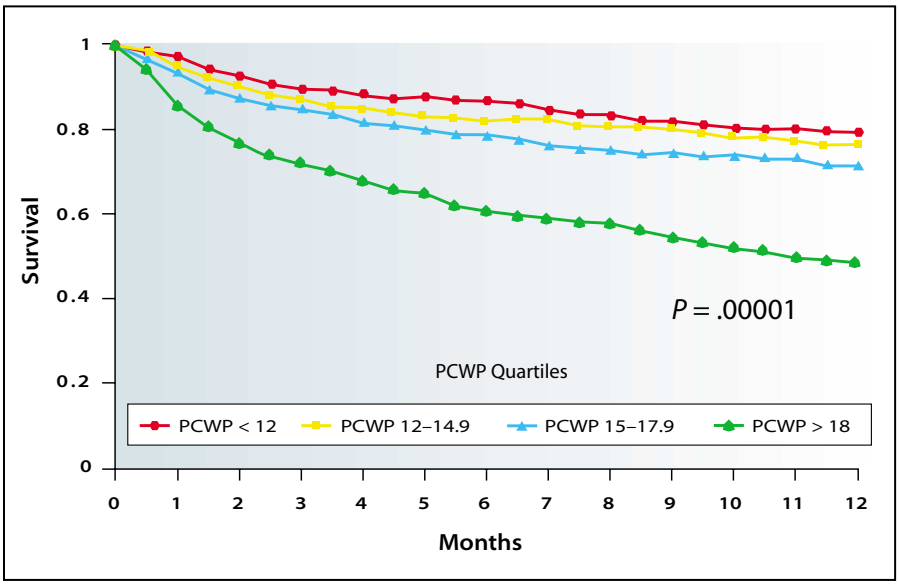

Figure 2. *Relationship between hemodynamic response and mortality in heart failure. Kaplan-Meier survival curves for the 1156 patients by quartiles of primary capillary wedge pressure (PCWP). On multivariate analysis, PCWP was an independent predictor of mortality, but resting cardiac index was not.*

inotropic agents to improve cardiac index. Intravenous inotropic agents, as a result of their primary mechanisms, increase cardiac index and decrease systemic vascular resistance and indirectly decrease ventricular filling pressures. If the most important hemodynamic target in decompensated heart failure is cardiac index, these agents would be preferred.[5] As diuretics reduce extracellular volume, these agents would be preferred if this were the predominate mechanism of decompensation. Intravenous vasodilators, as a result of their primary mechanisms, decrease ventricular filling pressures and systemic vascular resistance, and indirectly increase cardiac index. If the most important hemodynamic target in decompensated heart failure is ventricular filling pressures, these agents would be preferred.[5]

Because the dominant symptoms of ADHF are those of congestion, relief of resting symptoms requires reduction of elevated ventricular filling pressures.[3] The symptom of dyspnea correlates more closely with left ventricular filling pressure than any other hemodynamic parameter. Benefits of reducing filling pressures extend, however, beyond initial symptomatic improvement. Mitral regurgitation usually takes more than 50% of total left ventricular stroke volume in patients symptomatic at rest and is most effectively reduced and redistributed forward by therapies that reduce left ventricular filling pressures and systemic vascular resistance.[9] Elevated filling pressures not only increase myocardial oxygen consumption, but also compromise the gradient for myocardial perfusion, both of which may lead to ischemia. Neurohormonal activation is also strongly related to stretch of the ventricles, and hence levels of left ventricular filling pressures.[5,10]

Persistent elevation in left ventricular filling pressures has been associated with an increased risk of progressive heart failure death, sudden death, and overall mortality in patients hospitalized with decompensated heart failure. In a study of 1156 patients hospitalized with ADHF due to systolic dysfunction (mean left ventricular ejection fraction [LVEF] 0.21) and treated with intravenous vasodilators and diuretics, the achievement of near-normal left ventricular filling pressures (PCWP < 14 mm Hg) resulted in a 1-year survival rate of 78.2%, compared to only 48.4% in patients with persistently elevated ventricular filling pressures (P = .0001) (Figure 2).[8] Hemodynamic measures at baseline such as right atrial pressure, pulmonary arterial pressure, systemic arterial pressure, cardiac index, and heart rate were not predictive of mortality in this patient population. Multivariate analysis showed high pulmonary wedge pressure (P = .001), low serum sodium (P = .002), increased left ventricular end diastolic dimension (P = .01), and low peak oxygen consumption on cardiopulmonary exercise testing (P = .001) to be independent predictors of total mortality at 1 year.

Despite decreased cardiac index being a central feature of decompensated heart failure, changes in cardiac index have not been shown to be predictive of subsequent outcome.[8,11] It has also been shown that even at levels below symptom threshold, elevated PCWP predicts worse outcome in heart failure patients.[8] B-type natriuretic peptide (BNP) is elevated in heart failure patients and closely correlates with elevated PCWP. BNP levels have also been shown to be an independent predictor of rehospitalization or death in patients hospitalized with heart failure.[12] Whether by direct hemodynamic measurement, inferred by symptoms of orthopnea, or assessed with a biologic assay, elevated left ventricular filling pressures are associated with adverse clinical outcomes and increased mortality.[5]

An ideal agent for ADHF would be

one that rapidly reduces PCWP, and as a result relieves symptoms and hypoxia, results in balanced arterial and venous dilation, promotes natriuresis, lacks direct positive inotropic effects, and does not result in reflex neuroendocrine activation (Table 1). A summary of the effects of intravenous medications for ADHF is shown in Table 2.

Table 1
Characteristics of an Ideal Agent for Acutely Decompensated Heart Failure

Vasodilation (venous and arterial)
Rapidly decreases ventricular filling pressures
Rapidly decreases symptoms of congestion
Does not increase heart rate or directly increase contractility (decreases myocardial oxygen demand)
Is not proarrhythmic
Has no tachyphylaxis
Provides neurohormonal suppression
Promotes diuresis/natriuresis
Is conveniently dosed (can be used with or without invasive hemodynamic monitoring)

Treatment Strategies

Intravenous Loop Diuretics

Despite the fact that they have been used for many decades as front-line therapy in patients with acutely decompensated heart failure, only a few studies have examined the role and effect of intravenous loop diuretics.[4] Acute studies have shown that intravenous furosemide causes a significant decrease in PCWP and right atrial pressure, which is partially related to venodilation and partially due to diuresis.[4] There is, however, a concomitant decrease in stroke volume, increased systemic vascular resistance, and pronounced activation of neurohumoral activation.[13] Increases in renin-angiotensin-aldosterone system activation and increases in sympathetic activation (plasma norepinephrine levels) can be seen shortly after a single intravenous dose of furosemide.[13] In a trial of high-dose intravenous loop diuretics compared to treatment with low doses combined with an intravenous vasodilator, patients treated with high-dose furosemide did significantly worse in all primary and secondary outcomes measures, including being more likely to require mechanical ventilation (40% vs 13%; $P = .004$).[14]

Thus, whereas intravenous diuretics promote natriuresis and diuresis,

Table 2
Intravenous Agents for Acutely Decompensated Heart Failure

Agent	↑CO	↓PCWP	↑ or ↓BP	HR↑	↑Arrhythmia	Shorter Onset	Longer Offset	↑Diuresis
Dopamine								
Low (< 3 ng/kg/min)	0	0	0	0	0	+++	0	?
Mod (3–7 ng/kg/min)	+	0	↑	+	++	+++	0	?
High (7–15 ng/kg/min)	++	0	↑↑	++	+++	+++	0	0
Dobutamine	+++	+	0	+	++	+++	0	0
Isoproterenol	+++	++	0/↓	+++	+++	++++	0	0
Norepinephrine	++	0/+	↑↑↑	++	+++	++++	0	0
Epinephrine	++	0/+	↑↑↑	+++	+++	++++	0	0
Milrinone	++	+	↓	+	++	+	++	0
Nitroglycerin	+	++	↓↓	0	0	+++	0	0
Nitroprusside	+	++	↓↓↓	0	0	++++	0	0
Nesiritide (BNP)	+	++	↓	0	0	++	++	+

CO, cardiac output; PCWP, primary capillary wedge pressure; BP, blood pressure; HR, heart rate; BNP, B-type natriuretic peptide; ↑, increase; ↓, decrease; +, effect (number of and qualitatively associated with degree of effect); 0, no effect.

there is further deleterious neurohumoral activation and systemic vasoconstriction. This prevents normalization of ventricular filling pressures, limits relief of heart failure symptoms, and provides incomplete treatment, setting the stage for early rehospitalizations.

Morphine Sulfate

For many decades morphine has been a commonly used medication for treating ADHF in the emergency medicine setting. Morphine exerts effects that may be favorable in patients with ADHF. It reduces preload and to a lesser extent afterload (systemic vascular resistance) and heart rate. Morphine results in venodilation, decreases the sensation of dyspnea, and reduces sympathetic nervous system activation. These effects may result in a significant reduction of myocardial oxygen demand. However, morphine may result in central nervous system suppression and ventilatory depression. It may also aggravate bradycardia and hypotension (especially in the volume-depleted patient or in patients with right heart failure and pulmonary diseases). These unfavorable effects of morphine can be reversed by naloxone. The current recommended dose is 2–5 mg intravenously every 5–30 minutes. There are, however, no randomized trials to determine the relative benefits and risks with this agent.

In a recent retrospective analysis, the use of morphine sulfate in the ED for pulmonary edema was associated with increased need for intensive care unit (ICU) admission and mechanical ventilation.[15] Thus the role of morphine sulfate in treating ADHF is not fully defined.

Inotropic Agents

The strategy of using intravenous inotropic therapy to reverse decompensation in patients presenting with ADHF primarily targets a physiologic parameter that has not been associated with symptoms or improved clinical outcome (resting cardiac index). As a result, inotropic therapy would not be expected to reduce symptoms or improve patient outcome. Studies with intravenous inotropic agents have shown that use of these agents has been associated with increased risk of adverse events and, in some trials, increased mortality.[16]

The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial studied a 48-hour infusion of milrinone (0.5 μg/kg/min) in 949 patients hospitalized with acutely decompensated heart failure.[17] The use of the inotropic agent milrinone did not reduce length of stay and was associated with a significant increase in adverse events compared to placebo (12.6% vs 2.1%; $P < .001$) and a trend for increased mortality (3.8% vs 2.3%). Dobutamine is less likely to cause hypotension and is much less expensive than milrinone but also increases heart rate and of risk of arrhythmias. Low-dose infusion of dopamine is frequently utilized to improve renal blood flow and diuresis, but clinical trials have failed to demonstrate increases in urine output.

The use of positive inotropic agents also carries with it a risk of aggravating ischemia and arrhythmias. The weaning of inotropic support is frequently done slowly, potentially contributing to a more prolonged hospitalization. Another major limitation of inotropic therapy is the complexity of adjusting oral regimens as infusions are weaned. Prolonged physiologic effects of these infusions during hospitalization may mask inadequacy of the diuretic regimen and intolerance to vasodilator doses, setting the stage for readmission.[3] There is also concern that use of inotropic agents during admission for decompensated heart failure may create inotropic dependence. Trials with outpatient use of dobutamine, milrinone, vesnarinone, enoximone, and xamoterol have shown increased mortality compared to placebo.[16]

Although the limited benefits of inotropic infusions do not justify the risks in the majority of patients presenting with decompensated heart failure, this therapy can be life-saving in patients with cardiogenic shock. For chronic decompensation, brief inotropic therapy may be appropriate in those patients with high baseline blood urea nitrogen levels who have not demonstrated effective diuresis in response to vasodilators, natriuretic peptides, and intravenous loop diuretics.[3]

The early hemodynamic effects achieved with intravenous vasodilators and diuretics can be maintained in the long term with the use of an oral heart failure medical regimen.

Intravenous Vasodilators

A strategy of using intravenous vasodilators to reverse acute heart failure decompensation is more physiologically rational in that it primarily targets elevated ventricular filling pressures and elevated systemic vascular resistance.[5] The use of intravenous vasodilators has not been associated with worsening myocardial ischemia or the precipitation of

ventricular arrhythmias and actually reduces myocardial oxygen consumption.[3] Intravenous vasodilators also allow for easier and more rapid transition to an oral angiotensin-converting enzyme (ACE) inhibitor and diuretic regimen.[18] The early hemodynamic effects achieved with intravenous vasodilators and diuretics can be maintained in the long term with the use of an oral heart failure medical regimen. The significant reduction (and near-normalization) of ventricular filling pressures achieved with intravenous vasodilators and diuretics within 24 to 72 hours in patients with severe decompensated heart failure has been shown capable of maintenance over the next 8 months with an oral regimen of ACE inhibitors and diuretics.[19]

Thus intravenous vasodilators can promote the rapid reversal of the decompensated state with normalization or near-normalization of resting hemodynamics that can then be maintained in the long term with an oral heart failure medical regimen. When combined with a heart failure disease management program, this approach has been associated with an 85% reduction in hospitalization and improved functional capacity compared to conventional management.[20] The vasodilator strategy can also facilitate the more rapid initiation and titration of other survival-enhancing heart failure medications such as μ-blockers by promoting the rapid resolution of volume overload.

Sodium nitroprusside is a potent direct nitrovasodilator. Filling pressures are lowered rapidly through venous and arterial vasodilation, with increases in cardiac output, which in turn improve response to intravenous diuretics.[11] This use of nitroprusside is limited in that administration requires invasive monitoring using a pulmonary artery catheter in a cardiac care unit setting with nurses well trained in its use and staffed to perform frequent dose titration. The optimal hemodynamic profile achieved with nitroprusside can then be maintained by adjusting oral vasodilator agents, usually combinations of ACE inhibitors, nitrates, and sometimes hydralazine, as nitroprusside is weaned.[19] Monitored nitroprusside infusion rarely causes symptomatic hypotension but is occasionally complicated by cyanide toxicity, the risk of which increases with dose, duration, and hepatic dysfunction.

Nesiritide possesses many of the characteristics of an ideal agent for treating ADHF.

Intravenous nitroglycerin causes both arterial dilation and venodilation in patients' acutely decompensated heart failure. There has been little in the way of clinical trials to evaluate intravenous nitroglycerin for this purpose. The Vasodilation in the Management of Acute Congestive heart failure (VMAC) trial showed a reduction in filling pressures with intravenous nitroglycerin compared to placebo when added to standard care.[21] Side effects of headache can limit the use of this agent. Dosing can be guided with or without invasive hemodynamic monitoring. Frequent uptitration in dose is required to achieve meaningful symptomatic response. Early tachyphylaxis has been seen with higher doses of intravenous nitroglycerin.[22] The effect of nitroglycerin on neurohormonal activation has not been well studied. Successful transition to an effective oral vasodilator regimen is relatively straightforward.

Natriuretic Peptides

Natriuretic peptides function as balanced vasodilators while also producing some degree of natriuresis and lusitropy. Nesiritide, a recombinant human BNP, has recently been evaluated in a compendium of clinical trials in ADHF and subsequently approved for clinical use.[21,23] Nesiritide possesses many of the characteristics of an ideal agent for treating ADHF (Table 1). The intravenous administration of nesiritide has been shown to produce favorable hemodynamic effects, including balanced vasodilation associated with a rapid improvement in heart failure clinical symptoms. Nesiritide also reduces levels of deleterious neurohormones such as norepinephrine, aldosterone, and endothelin-1.[23] A dose-related reduction in ventricular filling pressures and augmentation of left ventricular stroke volume due to afterload reduction have been noted following both bolus administration and continuous infusion of a fixed nesiritide dose.[21] These effects appear to be sustained during continuous administration over 48 hours, and nesiritide compares quite favorably to nitroglycerin, with more rapid reduction in PCWP and fewer side effects. Indeed, the VMAC trial demonstrated that a 2 μg/kg intravenous bolus given over 1 minute followed by a fixed infusion of 0.01 μg/kg/min rapidly, efficiently, and safely reduced PCWP while improving self-reported dyspnea index scales in patients both with and without pulmonary artery catheters to monitor their central hemodynamics.[21] In this study, nesiritide was added to standard therapy (including dobutamine, dopamine, and parenteral diuretics)

in patients hospitalized with acutely decompensated congestive heart failure due to a wide variety of causes. Results indicated that nesiritide achieved greater hemodynamic and clinical benefits compared to intravenous nitroglycerin, with fewer adverse effects.

Nesiritide may be started simultaneously or just prior to intravenous diuretic therapy at the time of initial presentation in patients presenting with acutely decompensated heart failure. Nesiritide may be administered in conjunction with dopamine or inotropic agents such as dobutamine if the use of those agents is otherwise indicated. Nesiritide has been shown to be safely administered in monitored settings such as EDs, observation units, inpatient telemetry or step-down units and does not require ICU monitoring.[21] Proarrhythmic effects were not seen, and there is evidence of a much lower rate of ventricular arrhythmias with nesiritide treatment as compared to treatment with inotropic agents such as dobutamine.[24] Symptomatic hypotension, as evidenced in the comparative trial VMAC, was seen in only 4% of nesiritide-treated patients as compared to 5% treated with nitroglycerin.[21] The dose-limiting side effect of nesiritide is hypotension. With a half-life of 15–20 minutes, nesiritide should not be titrated at frequent intervals as is done with other intravenous agents that have a shorter half-life.

Rapid reversal of the decompensated state may also allow for shorter

Main Points

- The two fundamental hemodynamic parameters for rapid assessment of acutely decompensated heart failure relate to presence or absence of elevated filling pressures (wet or dry) and perfusion that is adequate or critically limited (warm or cold); rales are absent in more than 80% of patients with chronically elevated filling pressures due to compensation of the pulmonary lymphatics.
- Persistent elevation in left ventricular filling pressures has been associated with heart failure symptoms, an increased risk of progressive heart failure death, sudden death, and overall mortality in patients hospitalized with decompensated heart failure.
- In a trial of high-dose intravenous loop diuretics compared to treatment with low doses combined with an intravenous vasodilator, patients treated with high-dose furosemide did significantly worse in all primary and secondary outcomes measures, including being more likely to require mechanical ventilation.
- Morphine reduces preload and to a lesser extent afterload (systemic vascular resistance) and heart rate, results in venodilation, decreases the sensation of dyspnea, and reduces sympathetic nervous system activation; however, it may result in central nervous system suppression and ventilatory depression.
- Studies with intravenous inotropic agents have shown that use of these agents has been associated with increased risk of adverse events and, in some trials, increased mortality; brief inotropic therapy may be appropriate in those patients with high baseline blood urea nitrogen levels who have not demonstrated effective diuresis in response to vasodilators, natriuretic peptides, and intravenous loop diuretics.
- Intravenous vasodilators can promote rapid reversal of the decompensated state with normalization or near-normalization of resting hemodynamics that can then be maintained in the long term with an oral heart failure medical regimen; combined with a heart failure disease management program, this approach has been associated with an 85% reduction in hospitalization and improved functional capacity compared to conventional management.
- Intravenous administration of nesiritide has favorable hemodynamic effects including balanced vasodilation associated with a rapid improvement in heart failure clinical symptoms; nesiritide also reduces levels of deleterious neurohormones such as norepinephrine, aldosterone, and endothelin-1.
- A dose-related reduction in ventricular filling pressures and augmentation of left ventricular stroke volume due to afterload reduction have been noted following both bolus administration and continuous infusion of a fixed nesiritide dose; these effects appear to be sustained during continuous administration over 48 hours.
- Nesiritide compares quite favorably to nitroglycerin, with more rapid reduction in primary capillary wedge pressure and fewer side effects.
- Hemodynamic optimization with rapid reduction in left ventricular filling pressures and vascular resistance appears to be the most important target for therapy to achieve clinically stability as well as reduce the long-term risk of fatal decompensation and sudden death in heart failure.

duration of intravenous therapy and potentially impact length of ICU stay. In a study of 262 patients with decompensated heart failure comparing patients treated with one of two doses of nesiritide (0.015 μg/kg/min and 0.03μg/kg/min) or dobutamine added to standard care, the duration required for continued infusion of nesiritide therapy was significantly shorter.[25] The duration of study drug averaged 88 hours in the dobutamine group versus 51 hours ($P < .05$) in the nesiritide 0.015 μg/kg/min group and 44 hours ($P < .05$) in the nesiritide 0.030 μg/kg/min group. More rapid and complete reduction in elevated filling pressures may reduce the risk of recurrent decompensation and rehospitalization. In the same study, fewer nesiritide patients were readmitted for all causes, as well as for heart failure. During the 21-day follow-up period, there was a 20% rate for all readmissions in the dobutamine group versus 8% ($P < .05$) and 11% in the nesiritide 0.015 μg/kg/min and 0.030 μg/kg/min groups, respectively.[25] Nesiritide use also resulted in substantially improved survival of decompensated heart failure patients over the next 6 months. It has thus been shown to result in lower health care costs and reduced mortality compared to dobutamine.

Nesiritide has been demonstrated to lead to sustained clinical benefits in a broad range of ADHF patients when added to standard treatment regimes. Nesiritide offers the clinical benefits of a more rapid and sustained hemodynamic effect with fewer adverse effects than alternative heart failure treatments such as nitroglycerin or dobutamine. The use of nesiritide represents an entirely new treatment approach to reversing ADHF and to facilitating optimization of the heart failure medical regimen.

Optimization of Oral Heart Failure Therapies

After reversal of acute decompensation, comprehensive neurohumoral blockade with ACE inhibitors, β-blockers, and aldosterone antagonists can then be initiated or the dose adjusted to further reduce disability, hospitalizations, and death from heart failure.[1] Nonpharmacologic therapy should also be optimized and patient education provided prior to hospital discharge.[1,20] When combined with a comprehensive heart failure disease management program, the strategy of using intravenous vasodilators to normalize ventricular filling pressure and oral heart failure medications to maintain these effects has been associated with an 85% reduction in hospitalization and has been proven to improve functional capacity as compared to conventional heart failure management.[20] By facilitating the rapid reversal of decompensation through the use of intravenous vasodilators or nesiritide in the initial management of patients presenting to the ED, earlier administration of other beneficial heart failure therapies such as β-blockers may occur, whereas initiation of these therapies is typically contraindicated in a decompensated state.

Clinical Implications

In patients presenting with acutely decompensated heart failure, elevated left ventricular filling pressure and systemic vascular resistance directly contribute to fluid redistribution, pulmonary edema, and respiratory compromise. Although ventricular filling pressures have been shown to be highly predictive of symptoms and clinical outcomes, resting cardiac index has not. Focus on acute maximization of cardiac output led to therapies that increased mortality. Hemodynamic optimization with rapid reduction in left ventricular filling pressures and vascular resistance appears to be the most important target for therapy to achieve clinically stability as well as reduce the long-term risk of fatal decompensation and sudden death in heart failure.

There is thus compelling evidence supporting the use of vasodilators or natriuretic peptides (with or without intravenous diuretics) as opposed to inotropic agents or high-dose intravenous loop diuretic monotherapy in the ADHF patient, in the absence of cardiogenic shock. An ideal agent for ADHF is one that rapidly reduces PCWP, results in balanced arterial and venous dilation, promotes natriuresis, lacks direct positive inotropic effects, and does not result in reflex neuroendocrine activation. After rapid reversal of decompensation, comprehensive neurohumoral blockade can then be initiated to further reduce disability, hospitalizations, and death from heart failure. Use of effective pharmacologic treatment to optimize ED heart failure care can have a significant impact upon patient outcomes and upon resource utilization. ■

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