New Therapeutic Choices in the Management of Acute Congestive Heart Failure

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Patients with acute congestive heart failure generally present with profound fluid retention states and dyspnea due to pulmonary edema. If the condition is not aggressively and appropriately treated, irreversible cardiac decompensation may ensue, leading to cardiogenic shock, multiorgan failure, and death. Intravenous inotropic, vasopressor, and vasodilator therapies have proved effective in initial stabilization of acute heart failure decompensation, but these agents, particularly the traditionally used ones, are generally limited by side effects that can be egregious and include substantive ventricular arrhythmias. Dobutamine has largely replaced agents with rather profound toxicity, such as isoproterenol and epinephrine. The phosphodiesterase-inhibiting agent milrinone, having both vasodilator and inotropic properties, can produce tachycardia and significant ventricular arrhythmias, but has proven quite useful for seriously ill patients. Clinical trials of levosimendan have found a positive inotropic response when the drug is given parenterally; vasodilating properties are also evident. Clinical trials are under way to evaluate the potential benefits of endothelin receptor antagonists when given intravenously. Intravenous administration of nesiritide, a recombinant human B-type natriuretic peptide, has been shown to produce favorable hemodynamic effects, including balanced vasodilation associated with a rapid improvement in clinical symptoms.
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Acute congestive heart failure is a daunting problem. Patients generally present with profound fluid retention states and dyspnea due to pulmonary edema. If the condition is not aggressively and appropriately treated, irreversible cardiac decompensation may ensue, leading to cardiogenic shock, multiorgan failure, and death. Particularly problematic is the smothering sensation caused by the severe pulmonary edema.

Table 1
Intravenous Agents for Heart Failure—Traditional Choices

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

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

Though not formally defined, acute decompensated congestive heart failure is generally considered to be present when symptoms of heart failure develop over a period of hours or days in patients without a prior history of cardiac decompensation.[1] Patients may, however, have a history of prior cardiovascular disease and, in particular, evidence of ischemic heart disease or hypertension. Nonetheless, other etiologies may also be apparent, including acute valvular insufficiency (such as might occur in infectious endocarditis or aortic root dissection), acute myocarditis, severe and uncontrolled hypertension, and pulmonary embolism. Although most patients with acute decompensated congestive heart failure suffer from some degree of left ventricular systolic dysfunction, many patients with fairly normal ejection fractions present with acute heart failure decompensation. In particular, patients with underlying restrictive or hypotrophic myocardial disease are predisposed to acute decompensation.

If the condition is not aggressively and appropriately treated, irreversible cardiac decompensation may ensue.

Heart failure diagnosis and management guidelines have been published in a consensus document by the American College of Cardiology and the American Heart Association. The guidelines categorize patients presenting with acute heart failure into three major clinical groups: acute cardiogenic pulmonary edema, cardiogenic shock, and acute decompensation of chronic left ventricular dysfunction.[2] Although approaches to these groups of patients will be different, a rapid evaluation, diagnosis, and institutional therapy are imperative if morbidity and mortality are to be reduced. Traditionally, treatment has focused on the precipitating and underlying life-threatening conditions associated with acute heart failure decompensation, such as acute ischemic myocardial injury and complications of myocardial infarction (ventricular septal defect, cardiac tamponade from ventricular perforation, acute mitral valve insufficiency). However, in addition

Table 2
Intravenous Agents for Heart Failure—Emerging Choices

Agent	↑CO	↓PCWP	↑or↓BP	HR↑	↑Arrhythmia	Shorter Onset	Longer Offset	↑Diuresis
Toborinone (PDE III Inhib)	+++	++	↑↓	++	++++	+	+	0
Levosimendan (Ca^{++} Sens)	++	+	↓	++	0	+	+++	0
Tezosentan (ET Antag)	++	+	↓	0	0	++	0	0
Nesiritide (BNP)	+	++	↓	0	0	++	++	+

See Table 1 for core abbreviations; PDE, phosphodiesterase; CA^{++} Sens, calcium sensitizer; ET Antag, endothelin antagonist.

to addressing the underlying lesion, manipulation of the patient's hemodynamics is extraordinarily important to relieve symptoms and stabilize peripheral organ function.

Rather dramatic advances in pharmacologic support for acutely decompensated congestive heart failure have been made during the last several decades. Despite that fact, morphine, nitrates, and phlebotomy—remedies for acute pulmonary edema commonly used in the nineteenth century—are still used today. In the 1960s, acute therapies focused primarily on these agents, along with digitalis and diuretics. Indeed, furosemide first came available in the late 1960s.

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Intravenous inotropic, vasopressor, and vasodilator therapies, introduced in the 1970s, proved effective in initial stabilization of acute heart failure decompensation, with the development of dobutamine being an extraordinarily important step in patients with cardiogenic shock, as this drug has largely replaced agents with rather profound toxicity, such as isoproterenol and epinepherine.[3] The phosphodiesterase-inhibiting agent milrinone, having both vasodilator and inotropic properties, was the last drug formally approved by the U.S. food and Drug Administration for use in patients with decompensated congestive heart failure. As with beta adrenergic agents, a rate-limiting factor for milrinone administration can be the production of tachycardia and significant ventricular arrhythmias. Nonetheless, this agent has proven quite useful for seriously ill decompensated congestive heart failure patients. Table 1 summarizes the hemodynamic and ancillary effects of traditional agents used during the management of acute decompensated congestive heart failure. This information should be compared to that contained in Table 2, which details the investigational agents currently being evaluated for use in a similar patient population.

New Agents for Acute Heart Failure

It should be stressed that there is no consensus regarding the relative importance of each therapeutic class of agents previously discussed in acute decompensated heart failure. Uncertainty in agent choice has been compounded by the fact that milrinone, the last drug introduced for these patients, was approved for this indication over one decade ago. There has been a growing interest in several new agents, some of which will undoubtedly come into common use.

Positive inotropic drugs. Levosimendan and toborinone have been studied in clinical trials of hospitalized decompensated congestive heart failure patients. Both agents have positive inotropic properties coupled with other features that distinguish them from dobutamine and milrinone. Levosimendan is currently available in some European countries.

It is uncertain whether toborinone will meet clinicians' expectations for a safe and effective drug.

Levosimendan induces a positive inotropic response when given parenterally, primarily by increasing the sensitivity of the myofilaments (specifically troponin-C) to intracellular calcium.[4] This option is independent of cyclic adenosine monophosphate (AMP) and thus elicits inotropy while avoiding many of the adverse effects commonly associated with cyclic AMP–dependent agents. Vasodilating properties are also evident with levosimendan, and this effect is mediated through inhibition of phosphodiesterase-III and by activation of potassium-dependent adenosine triphosphate (ATP) channels.[5] Furthermore, it has been suggested that levosimendan has lusitropic effects on the failing heart. These multiple mechanisms of action result in the expected hemodynamic changes during short-term intravenous administration to patients with severe heart failure. Noted has been a significant improvement in cardiac index (resulting primarily from increased stroke volume), reduction in systemic pulmonary vascular resistance, and reduced filling pressures with a slight increase in heart rate. Ventricular arrhythmias and tachycardia were noted more often at higher-dose infusion rates. Interestingly, some observations suggest that transient infusions of levosimendan may translate into a survival benefit in those with severe acute heart failure.[6] Interestingly, levosimendan has a longer-acting metabolite that may induce some of this benefit. Whether or not the observations made are relevant is highly contentious, and further large-scale clinical trials are being planned to define better the value of this agent in the management of decompensated heart failure. Certainly, one must be concerned about the tachycardia that has been noted.

Levosimendan induces a positive inotropic response when given parenterally.

Toborinone exerts positive inotropic activity and balanced vasodilation primarily through phosphodiesterase-III inhibition.[7] Evaluation of this compound has identified favorable hemodynamic benefits in heart failure during short-term intravenous administration and, particularly, rather profound increases in cardiac output and reductions in filling pressures and peripheral vascular resistance coincident with reduction in myocardial oxygen consumption.[8] Although toborinone, unlike other cardiotonic medications, does not appear to increase heart rate at hemodynamically effective doses, substantive ventricular arrhythmias have been noted that may be rate-limiting and may stop further consideration of this compound's development. This agent may be the most profound inotropic agent of all the so-called "inodilator" drugs studied to date.[9]

Endothelin receptor antagonists. Endothelin (ET-1) is a potent vasoconstrictor, which is elevated in patients with congestive heart failure.[10,11] ET-1 activates endothelin Type A and B receptors which are densely apparent on vascular smooth muscle and coronary endothelium. ET-1 levels have been shown to correlate with pulmonary vascular resistance in severe congestive heart failure, suggesting that this humoral agent mediates the reactive pulmonary hypertension seen in this condition. Clinical trials are under way to evaluate the potential benefits of endothelin receptor antagonists when given intravenously in treating acute decompensated heart failure. Tezosentan is a short-acting, parenteral, dual endothelin receptor antagonist. Because of its water solubility and short plasma half-life, this drug seems particularly promising.[12] Recently completed trials have demonstrated a significant reduction in pulmonary capillary wedge pressure and systemic pulmonary vascular resistance with this agent, while there is significant increase in cardiac output but no tachycardia or proarrhythmia.[13] These preliminary findings support a potential role for tezosentan in the treatment of acute heart failure; however, further studies are necessary to define more precisely dose-effect relationships and give guidance to best administration tactics and strategies.

Natriuretic peptides. Interestingly, not all new pharmacologic strategies are based on the use of "designer" drugs to block actions of potentially harmful counterregulatory humoral responses in heart failure (such as endothelin antagonists) or to stimulate intracellular modulators of contraction (such as toborinone); rather, another strategy seek to mimic seemingly beneficial counterregulatory effects of hormones secreted in response to cardiac congestion. Indeed, the concentration of circulating endogenous natriuretic peptides is known to increase in patients with congestive heart failure. These peptides are produced by

the myocardium in response to increased myocyte tension and wall stress, which is noted during end diastolic ventricular pressure rise. The degree of natriuretic peptide elevation correlates with disease severity.[14] The actions of endogenous natriuretic peptides partially counteract the harmful effects of other neurohormones that are elevated in heart failure, specifically renin, aldosterone, and norepinephrine.

Natriuretic peptides appear to be balanced vasodilators while also producing some degree of natriuresis and lusitropy. Nesiritide, a recombinant human B-type natriuretic peptide (BNP), has recently been evaluated in a compendium of clinical trials in acute and decompensated heart failure.[15,16] 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. 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 24 hours, and nesiritide compares quite favorably to standard inotropic and vasodilator therapy for heart failure, with a trend toward fewer side effects. Indeed, the Vasodilation in the Management of Acute Congestive heart failure (VMAC) trial recently demonstrated that a 2 μg/kg intravenous bolus given over 1 minute followed by a fixed infusion of 0.01 μg/kg/min will rapidly, efficiently, and safely reduce pulmonary capillary wedge pressure while improving self-reported dyspnea index scales in patients both with and without pulmonary artery catheters to monitor their central hemodynamics. 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 by a wide variety of causes. Results indicated that nesiritide achieved greater hemodynamic and clinical benefits compared to intravenous nitroglycerin, with fewer adverse effects. Particularly important has been the fact that nesiritide is not associated with an increase in heart rate or proarrhythmia.

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.

Summary

Heart failure's complexity and significant morbidity has generated broad interest in potential new therapeutic modalities, particularly for the unstable decompensated patient requiring hospitalization. A wide spectrum of old and new intravenous vasodilating and inotropic drugs is now available to correct specific hemodynamic abnormalities. These agents, particularly the traditionally used ones, are generally limited by side effects that can be egregious and include substantive ventricular arrhythmias. Interestingly, new drug therapies in the acutely decompensated patient are targeting more specific hemodynamic and neurohormonal perturbations. These agents should be coupled with advancements in medical technology that have improved our ability to monitor and continuously evaluate the patient with severe hemodynamic compromise, in particular implantable arrhythmia monitoring devices and hemodynamic sensing recorders. Nonetheless, advances in technological support and treatment options for acute heart failure have not simplified its management. The significance of the initial clinical assessment and treatment plan for the decompensated patients

Main Points

- Most traditional parenteral agents for acutely decompensated heart failure focus on vasodilating and/or inotropic effects.
- Parenteral agents for decompensated heart failure having inotropic effects generally also produce significant cardiac arrhythmias.
- Some of the newer agents for decompensated heart failure attempt to mimic the beneficial counterregulatory effects of naturally occurring hormones noted in patients with congestive heart failure (natriuretic peptides).
- When patients with congestive heart failure develop acute decompensation mandating hospitalization, an individualized approach will be required, with choice of newer agents dictated by the hemodynamic response desired.

must be emphasized. Due to the diverse nature of acute heart failure symptoms and complexity of the syndrome, there is no straightforward "cookbook" approach to the pharmacologic management of the decompensated heart failure patient. Nonetheless, newer therapeutic choices will certainly add to our abilities to attenuate this difficulty. ■

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