EDITORIAL COMMENT
Acute Decompensated Heart Failure

The Shrinking Role of Inotropic Therapy*

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Acute decompensated heart failure is among the most common indications for hospitalization in the U.S. and results in approximately one million hospitalizations annually (1). Although consensus guidelines provide evidence-based strategies for the treatment of chronic heart failure, the current therapy of acute heart failure is largely empirical. The first priority of management is relief of symptoms. A variety of studies have shown consistent correlations between improvement in resting hemodynamics, particularly the reduction of elevated filling pressures, and improved symptom status during hospitalization and beyond (2). Intravenous vasodilators and positive inotropic agents both acutely lower filling pressures and enhance cardiac output. Although both drug classes are often viewed as “cornerstones” of treatment, considerable controversy exists about their relative benefits during hospitalization.

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In this issue of the Journal, Abraham et al. (3) help clarify the role of intravenous vasactive therapy for inpatient management of acute decompensated heart failure. The authors performed a retrospective observational analysis using data from the Acute Decompensated Heart Failure (ADHERE) national registry, which was designed to prospectively collect information on heart failure hospitalizations and clinical outcomes. More than 65,000 admissions were analyzed; patients who received either intravenous vasodilator therapy (nitroglycerin or nesiritide) or inotropic therapy (dobutamine or milrinone) were compared. The principal finding of the study was that short-term vasodilator therapy was associated with significantly lower inhospital mortality than positive inotropic treatment. A propensity score analysis was performed for each pair-wise comparison to adjust for potentially confounding differences in baseline clinical and demographic characteristics between treatment groups. This propensity score has been previously validated to produce relatively unbiased estimates of treatment effect in observational studies. Unadjusted in-hospital mortality varied widely, ranging from 4.1% for the entire cohort to as much as 14% for patients who received intravenous inotropes. Patients treated with either nitroglycerin or nesiritide had intermediate mortality rates of 4.7% to 7.1%. Adjusted inpatient mortality odds ratios of 0.59 and 0.47 were observed for nesiritide versus milrinone or dobutamine, respectively. Similarly, adjusted inpatient mortality odds ratios of 0.69 and 0.46 were noted for nitroglycerin therapy versus milrinone or dobutamine, respectively. Mortality did not differ between nesiritide and nitroglycerin therapy.

The impact of intravenous inotropic therapy during hospitalization recently has been investigated in two randomized controlled trials. In the Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbation of Chronic Heart Failure (OPTIME-CHF), Cuffe et al. (4) randomly assigned 951 hospitalized patients to a 48-h infusion of intravenous milrinone or placebo. The administration of milrinone was associated with a higher rate of early treatment failure, more sustained hypotension, and new atrial arrhythmias. A nonsignificant but higher number of deaths also was observed (3.8% vs. 2.3%; p = 0.19). The calculated in-hospital mortality odds ratio for placebo versus milrinone in the OPTIME-CHF study was 0.61, which is almost identical to the ADHERE study investigators’ findings. Further, in-hospital use of milrinone was associated with a trend toward higher 60-day mortality. Felker et al. (5) reported a significant interaction between heart failure etiology and outcome. Patients with an ischemic etiology that were treated with milrinone had a higher 60-day mortality (11.6%) than that observed in the nonischemic group (7.5%; p = 0.03) and a higher composite rate of death or rehospitalization (42% vs. 35%; p = 0.01). The authors conclude that milrinone should not be used routinely for patients with an exacerbation of heart failure (5).

The effect of nesiritide and dobutamine on short-term outcomes in acute heart failure was reported recently in an open-label, randomized, controlled trial by Silver et al. (6). Hemodynamically unstable patients who required immediate inotropic or vasopressor support or whose initial systolic blood pressure fell to <90 mm Hg were excluded from the trial. Although no difference was noted in hospital length of stay, a trend toward fewer readmissions was observed for nesiritide treatment. Importantly, six-month mortality was lower for patients treated with low-dose nesiritide (18%) compared with those treated with dobutamine (31%) (6). These two trials teach the important lesson that even short-term exposure to positive inotropic agents that act by increasing intracellular cyclic AMP during periods of acute decompensation increase risk after hospital discharge. This conclusion is not entirely surprising; the myocardium is further stressed by markedly altered hemodynamics and further activation of neurohormones, cytokines, and oxygen-free radicals. Inotropic stimulation during a period of myocardial energy depletion may induce cell death by

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ischemia or apoptosis (7). This message is again reiterated by the ADHERE study results.

The ADHERE study results should not be over-interpreted to conclude that milrinone and dobutamine have no role in the contemporary treatment of acute heart failure. Although it is clear that their routine use is not warranted, these agents can be lifesaving for patients with rapidly progressive hemodynamic collapse (2,7). Patients who present with obtundation, anuria, or lactic acidosis may only respond to inotropic therapy, which should be used until the cause of shock is determined and definitive therapy implemented. Nohria et al. (2) have confirmed the utility of a two-minute bedside assessment of hemodynamic profiles for patients with advanced heart failure. The majority of patients enrolled in clinical trials and virtually all patients in the ADHERE study had evidence for elevated filling pressures and preserved end-organ perfusion (“warm and wet” profile). The optimum management for those individuals with elevated filling pressures and significant hypoperfusion remains unknown. Many are unable to tolerate intravenous vasodilators and may, in theory, benefit from the transient use of newer positive inotropic agents that increase contractility without enhancing intracelullar cyclic AMP, such as levosimendan and toborinone, which act by increasing myocardial sensitivity to calcium (8).

More accurate risk profiling of hospitalized patients also may guide future treatment. Felker et al. (9) reported predictors of a composite end point of death or rehospitalization within 60 days of hospital discharge were the number of previous hospitalizations for heart failure, azotemia, lower systolic blood pressure, anemia, and a history of percutaneous coronary intervention.

The ADHERE study represents the largest hospitalized population with decompensated heart failure to be studied prospectively. Unlike clinical trials, the reported experience represents “real-world” contemporary management. It includes both systolic and diastolic etiologies of heart failure, an older population than typically is enrolled in clinical trials, a higher percentage of patients with diabetes, and a large percentage of patients with impaired renal function. Importantly, although the focus of this study was a comparison of intravenous vasoactive agents, it should be noted that more than 75% of the patients were treated with enhanced diuretic therapy alone.

Despite its considerable strengths, several limitations need to be acknowledged. The study was uncontrolled and observational in nature. Despite careful and statistically validated methodologies, it remains possible that severity of illness was not adequately controlled for by risk adjustment modeling. In addition, a surprisingly small percentage of patients were receiving vasodilators at study entry (angiotensin-converting enzyme inhibitors, 44%; angiotensin receptor blockers, 12%). Although few patients presented with de novo heart failure, it remains possible that the observed beneficial effects of intravenous vasodilators may have been greater than that routinely achievable when acute heart failure develops despite maximal oral vasodilator therapy. Finally, milrinone or dobutamine may have been “reserved” for patients who failed to respond to more conventional therapies. Median time to initiation of diuretic therapy was 9.5 h, 15.9 h for nitroglycerin, 30 h for nesiritide, 46 h for dobutamine, and 54 h for milrinone. It is conceivable that positive inotropic agents were viewed as drugs of last resort. It is also possible that the delay in initiating these drugs may have contributed to worse survival.

Clinical implications. The treatment of acute decompensated heart failure among hospitalized patients should begin initially with increased diuretics. Most patients (>70%) will respond to this treatment alone. For the minority of patients in whom intravenous vasodilator therapy is considered, vasodilator treatment using nitrroglycerin, nesiritide, or possibly nitroprusside (which was not evaluated), appears to be the safest and most effective treatment option for patients who lack hemodynamic compromise. Intravenous inotropic support should be reserved for those patients with marked hemodynamic compromise, cardiogenic shock, or evidence for end-organ hypoperfusion. The optimum treatment for patients with cardiorenal syndromes and those identified as “high risk” remains to be determined. Although observational studies such as ADHERE study are useful in assessing current therapeutic practices, there is an urgent need for controlled trials in this growing patient population. Future practice guidelines for treatment of acute heart failure must be based upon more complete understanding of its pathophysiology and an evidence-based approach substantiated by prospective controlled trials. Hopefully, the treatment of acute decompensated heart failure during the next decade will become as rigorously defined as current outpatient therapy of the chronic heart failure syndrome.

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