Clinical Use of Inotropic Therapy for Heart Failure: Looking Backward or Forward?
Part I: Inotropic Infusions During Hospitalization

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Use of Inotropic Agents During Hospitalization

Critical Support Until Definitive Therapy

Inotropic therapy is occasionally required on a truly emergent basis for patients with evidence of critical hypoperfusion, such as obtundation or lactic acidosis. Such patients require immediate institution of inotropic therapy until the cause of shock is determined and definitive therapy implemented. The benefits and risks are most immediate in this situation. Acute stimulation of contractility leads to increased cardiac output and increased blood pressure for distribution to organs and tissues. Blood pressure can be further increased by those agents with α-receptor–mediated peripheral vasoconstriction. The degree to which filling pressures decline depends not only on contractility but also on the complex interactions between venous return, atrioventricular valve regurgitation, diastolic function, and peripheral vasoconstriction. Increased contractility and heart rate increase myocardial oxygen demand, which may on the other hand be decreased by reduction in decreased ventricular volumes and wall stress. The gradient for myocardial oxygen delivery will increase with better blood pressure and reduction of intraventricular filling pressures. Inotropic agents can trigger atrial and ventricular tachyarrhythmias directly and through hemodynamic effects.

There are few trial data to guide care in this setting. The choice of inotropic therapy for emergency situations is limited to agents that will support the blood pressure, the first choice generally being dopamine in medium to high doses, in which pressor effects may dominate (5 to 25 μg · kg⁻¹ · min⁻¹). This agent increases contractility and heart rate primarily through cardiac β-receptors and vasoconstriction through peripheral α-receptors at these doses. Peripheral vasodilation can occur to a modest degree with dobutamine and to a major degree with milrinone, so these agents are unlikely to improve this situation (Figure 1). If blood pressure cannot be maintained acutely with increasing doses of dopamine, epinephrine can be used as a more potent agonist for both β- and α-receptors. Norepinephrine is occasionally used when abnormal vasodilation is suspected, because of its slightly greater degree of peripheral vasoconstriction, but the risk of renal and peripheral ischemic injury may also

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Current Uses of Inotropic Agents in Heart Failure: Possible Trials

Therapy during hospitalization

- Critical support until definitive therapy (cardiogenic shock)
  - Placebo-controlled trial unlikely because of perception of immediate benefit from initiation, high risk from progressive shock, and heterogeneity of population
- Support until resolution of other conditions
  - Recovery from sustained tachyarrhythmia or infarction
  - Noncardiac illness, eg, pneumonia, gastrointestinal bleed
  - Recovery from noncardiac surgery
  - Trial of aggressive therapy to increase oxygen delivery in medical intensive care unit showed no obvious benefit. No trials of therapy aimed at normal cardiac output in this setting, in which it would be difficult to define homogeneous population.
- Resolution of congestion with apparent hypoperfusion (without shock)
  - Placebo-controlled and active control trials feasible with allowance for crossover to active therapy, would require consistent application of clinical criteria to ensure compromised population
  - Placebo-controlled trials feasible with allowance for crossover to active therapy
  - Comparison of 2 active therapies feasible, eg, inotropic agent compared with specific intervention for renal function or direct fluid removal
- Routine use for heart failure hospitalization without complicating features
  - One trial successfully completed that demonstrated increased adverse events without benefit. Other trials feasible in different patient cohorts.
- Intermittent outpatient therapy
  - Placebo-controlled and active comparison trials feasible; previous experience warrants review.
- Chronic therapy "until . . ."
  - Bridging until cardiac transplantation
    - Comparison trial of 2 active therapies feasible, with well-defined crossover options
    - Destination: end of life
    - Placebo-controlled drug trial probably not compatible with compassionate care. Comparison trial of 2 approaches could be considered, with liberal allowance for changing patient preferences

be greater. Because of the high risks of tachyarrhythmias, myocardial ischemia, and compromise of peripheral circulation, use of epinephrine or norepinephrine is generally limited to immediately life-threatening situations. Boluses or infusions of calcium may also help to maintain a detectable blood pressure over a period of minutes until definitive intervention. As these agents are being initiated, mechanical circulatory support should be arranged in appropriate candidates.

When shock is determined to be cardiogenic, the most likely causes are acute myocardial infarction, fulminant myocarditis, or acute noncardiogenic conditions such as pulmonary embolus, sepsis, or hemorrhage superimposed on left ventricular dysfunction. Although there is concern about potential aggravation of ischemia by inotropic agents in the setting of infarction, critical hypotension itself further compromises myocardial perfusion and markedly elevated left ventricular filling pressures both increase oxygen requirement and further decrease coronary perfusion gradient. In this setting, it is generally assumed that the benefits of hemodynamic improvement can outweigh the risks of inotropic therapy.

When hypotension is not immediately life-threatening, dobutamine, which also acts through β-adrenergic receptors to increase cAMP production (Figure 2), would generally be the first choice if inotropic support is necessary to improve cardiac output in an urgent setting. Stimulation of peripheral β-receptors with minimal opposing α-receptor stimulation tends to lower systemic vascular resistance slightly. Milrinone and other phosphodiesterase inhibitors increase cAMP by inhibiting its breakdown (Figure 2) and cause greater peripheral vasodilation. The choice between dobutamine and milrinone is often influenced by the perceived balance between greater increase in heart rate and myocardial oxygen consumption with dobutamine but greater risk of hypotension with milrinone (Figure 1), although some experiences suggest acute effects to be similar. The choice of agent has also been influenced by the higher cost of milrinone and the prolonged duration of action. Although the pharmacological half-life is 2 to 4 hours, it is prolonged by renal dysfunction. The deterioration after discontinuation of milrinone is often not maximally apparent until many hours later, as opposed to the rapid loss of dobutamine effect.

When cardiac output remains severely reduced with vasoconstriction despite increasing doses of dobutamine, the addition of milrinone may bypass the β-receptors that become downregulated by chronic heart failure and further downregulated by prolonged administration of β-agonists. Milrinone should only be initiated, however, when blood pressure is adequate to tolerate vasodilation. It has been suggested that patients undergoing chronic β-adrenergic blockade may respond better to milrinone than to dobutamine when inotropic support is required. Cardiac output response to increasing doses of dobutamine has often been achieved, however, even in the presence of chronic therapy with β-blocking agents.

Support Until Resolution of Other Conditions

The majority of patients receiving inotropic infusions for heart failure present a less urgent picture than above but have deteriorated as the result of a potentially reversible condition (Table). This condition may be one other than the heart failure itself, such as noncardiac surgery, pneumonia, or myocardial depression after prolonged ventricular tachyarrhythmia. Inotropic therapy is provided with the assumption that recovery will be facilitated by enhancement of cardiac output, either because cardiac output is low or because demands are high. Stimulation to levels of cardiac output >4.5 L · min⁻¹ · m⁻² did not improve outcomes for multiple diagnoses in medical intensive care units. When used now in these settings, inotropic therapy for patients with exacerbated heart failure is generally titrated only to approach normal cardiac output. Data regarding hemodynamic monitoring in critical care units and postsurgery units have raised concern that the higher mortality in monitored patients may reflect not just baseline severity of illness but also the overzealous use of inotropic therapy to treat numerically low cardiac output in clinically stable patients. There are no trials that specifically address the use of inotropic therapy in these conditions. Definition and inclusion of a sufficiently homogeneous
population and uniform criteria for crossover to inotropic therapy would probably not be feasible.

**During Hospitalization for Exacerbation of Chronic Heart Failure**

**Congestion and Apparent Hypoperfusion**

Hospitalizations for decompensation of chronic heart failure typically occur with elevated intracardiac filling pressures and circulating volume. Effective diuresis to relieve congestion is a key component of therapy. For triage and initiation of therapy at the time of admission, patients may be categorized functionally as having clinically adequate perfusion (wet and warm) or evidence of low resting perfusion (wet and cold), usually suspected because of a narrow pulse pressure, cold extremities, or both. The “wet and cold” patients with clinical evidence of low perfusion have longer hospital stays and higher numbers of subsequent events. Current consensus is that such patients generally require therapy in addition to diuretics to restore compensation.26
Inotropic Versus Vasodilator Therapy?

Many patients presenting with low cardiac outputs in this setting have markedly elevated systemic vascular resistance in addition to high intracardiac filling pressures, even when the systemic blood pressure is low. If a decision has been made to add an intravenous vasoactive agent in addition to diuretics, the first decision is whether to use a direct vasodilator or an inotropic agent to improve forward flow and perfusion.

Cardiac output will generally be increased both by intravenous vasodilators and by inotropic infusions when vasoconstriction is present. This is consistently seen in advanced heart failure when filling pressures are high and cardiac index is low, even when systolic blood pressures are below 95 mm Hg. Improved hemodynamics can decrease neurohormonal stimulation without specific neurohormonal antagonists. Cardiac index may be further increased by inotropic agents, particularly when systemic vascular resistance is not markedly elevated. Whether inotropic agents or vasodilators are used, the resulting improvement in cardiac output and filling pressures is associated with improvement in symptoms and functional capacity. Relief of resting symptoms may reflect largely the decrease in filling pressures rather than the direct effect of changing cardiac output. Clinical improvement was similar during therapy with inotropic agents or the brain natriuretic peptide nesiritide in a patient population that could be enrolled in a randomized comparison. The mitral regurgitant fraction is often reduced by treatment with 

Figure 2. Simplified comparison of intravenous inotropic agents currently used in management of heart failure, in relationship to factors that most commonly determine choice of agents for individual patients. For many comparisons, controlled data are limited, conflicting, or absent on direct comparison between different agents. There is no attempt to show magnitude of relative differences.

Tachyarrhythmias related to intravenous treatment are sometimes referred to as "renal congestive.

Tachyarrhythmic events have been associated with both dobutamine and milrinone in clinical practice, which in part may reflect preferential use of these agents in patients with more severe compromise. These complications have been confirmed, however, in randomized trials of inotropic agents versus placebo or vasodilator infusions for heart failure. Hypotension occurs more commonly in patients taking vasodilators than in those taking dobutamine. For patients in whom intravenous vasoactive therapy was not believed to be essential, symptom relief was equivalent between milrinone and placebo infusions added to standard therapy, with more hypotension seen after milrinone.

However, the experience in the most compromised patients is uncontrolled. Randomized trials performed with and without inotropic infusions during heart failure hospitalizations have selected patients in whom intravenous therapy was not necessarily considered essential for management. These populations had average systolic blood pressures of 120 mm Hg with serum sodium of 138 mEq/L, which differs markedly from that exemplifying the "wet and cold" profile in a study of hospitalized patients (systolic blood pressure 103 mm Hg, sodium 136 mEq/L). There are few data to guide the choice of vasodilator versus inotropic therapy in the population for whom some additional therapy is deemed to be warranted. Design of such a trial in "wet and cold" patients would be feasible, requiring careful definition of criteria for crossover in both directions. Although there was primary concern that invasive hemodynamic monitoring was required for the vasodilator nitroprusside, both nitroglycerin and nesiritide have been used effectively with noninvasive blood pressure monitoring only. Thus, the limited availability of pulmonary artery catheter monitoring no longer restricts the selection of intravenous therapies or impedes a trial to compare them.

When intravenous inotropic infusions have been used, they can mask inadequacy of an oral regimen adjusted before discharge, particularly for agents with longer physiological half-lives, such as the phosphodiesterase inhibitors. If infusions have been used, it has been recommended that they be discontinued for at least 48 hours before discharge of the patient from hospitalization for heart failure. This time period may need to be longer to assess stability after weaning from milrinone because of its prolonged physiological half-life, as discussed above.

Congestion With Impaired Renal Responses

Some patients may appear to have adequate perfusion but fail to respond well during diuretic therapy. One contributing factor is low regional perfusion for the kidneys. The kidneys normally receive approximately 1 L of blood flow per minute, which declines by more than half as cardiac output decreases to levels that are still adequate for other organ function at rest. This reduction can be particularly deleterious for patients with impaired baseline renal function as a result of either chronic heart failure or other insults. Some degree of renal dysfunction is common in heart failure, particularly of long duration, and increasingly limits the adequacy of diuresis.

When the initial diuretic response is inadequate despite continued increases in intravenous boluses or infusions of loop diuretics and addition of metolazone, diuresis may frequently be enhanced by low-dose inotropic infusions. Facilitation of diuresis by inotropic therapy presumably reflects improved renal blood flow through modest increases in cardiac output. Although low doses of dopamine (1 to 3 μg·kg⁻¹·min⁻¹) are sometimes referred to as "renal
doses” because stimulation of renal dopaminergic receptors has been shown,9,10 they are usually accompanied by detectable increases in cardiac output in patients with heart failure, and they can be associated with arrhythmias and ischemia. In the heart failure population, the effects of these doses of dopamine and dobutamine appear quite similar and warrant similar monitoring for arrhythmias. Renal function improves in some patients during infusion of nitroglycerin or nitroprusside, which may occur more often when severe vasoconstriction is present at baseline. The improvement in renal function with vasodilators has been less predictable than with the inotropic agents, perhaps because of regional differences in vasodilator response. The newer agent nesiritide theoretically offers selective renal vasodilation in addition to systemic vasodilation to lower filling pressures, but this may be blunted in patients with heart failure, in whom a specific strategy for supporting renal function during diuresis has not been established.

In some patients, aggravated renal dysfunction appears only after diuresis. Although this has at times been attributed to reduction in cardiac output with “overdiuresis,” cardiac output, when measured, has usually not decreased from baseline and may have increased.37 The causes are more complex, relating to other cardiorenal interactions, perhaps through neurohormonal changes or direct vascular reflexes.37 Patients in whom inotropic therapy is needed for support of renal function after diuresis may require adjustment of other medications, such as ACE inhibitors. Patients without obvious reversible factors often have recurrent renal dysfunction after discontinuation of intravenous support. This is frequently cited as one of the conditions for apparent dependence on intravenous inotropic agents.38 Development of worsening renal function has been associated with more than a 2-fold risk of adverse events in the hospital and after discharge.37,38 It is not known whether any intervention in the hospital would improve this prognosis, but a randomized trial could conceivably be performed to compare 2 active therapies, such as medication versus direct fluid removal, for patients who have marked renal dysfunction at baseline or who develop it during diuresis.

Routine Use During Heart Failure Hospitalization
The majority of patients hospitalized with heart failure exacerbation do not have clinical evidence of hypoperfusion, presenting instead the “wet and warm” profile.25 Inotropic infusions have often been initiated at the time of hospitalization for heart failure for these patients even in the absence of specific concern regarding perfusion or impaired renal responses to diuretic therapy. It has been suggested that such infusions might shorten hospital stay, improve ability to titrate ACE inhibitors, and decrease subsequent readmissions.40,41 However, the impact of intravenous inotropic therapy has recently been investigated in a randomized, double-blind controlled trial of milrinone versus placebo infusions in 951 patients (OPTIME-CHF: Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure).35 This trial highlights the dilemma of establishing a basis of evidence on which to treat hospitalized patients, because the only patients who could responsibly be included were those not believed to require inotropic infusions. Furthermore, milrinone was not compared with placebo alone because therapy with vasodilators and diuretics could be freely adjusted in both groups. Nonetheless, the trial demonstrated that milrinone infusions had no impact beyond that of standard therapy on length of stay, discharge ACE inhibitor dose, or readmission. Symptom relief was rapid and sustained in both arms of the study. Milrinone infusion was associated during hospitalization with 11% incidence of hypotension (compared with 3% for placebo) and 5% incidence of atrial fibrillation (compared with 2% for placebo). Concern was also raised regarding slight trends for higher rates of ventricular tachycardia, myocardial infarction, and mortality that may have been more evident in patients with ischemic etiology of heart failure. Despite the general enthusiasm for providing inotropic therapy as an adjunct to standard therapy, only 9% of patients randomized to placebo infusion in this trial were subsequently considered to be treatment failures.

In some cases, outpatients on a chronic diuretic regimen inadequate to relieve chronic volume overload have been admitted periodically for an elective dobutamine “tune-up” or “holiday.” The 3-day infusion of dobutamine was suggested after the initial observation of tolerance with prolonged dobutamine administration.42 Analysis of endomyocardial biopsy samples after 3 days suggested improved mitochondrial structure and increased ATP/creatine ratio,43 which could have reflected inotropic stimulation or the reduction in wall stress that would also occur with diuresis and vasodilation. Further experience in 38 patients receiving one 3-day infusion (without controls) indicated clinical improvement in 84% at 2 days, 59% at 4 weeks, and 43% at 10 weeks.44 Subsequent experience also described prolonged improvement after brief therapy with phosphodiesterase inhibitors.45 These studies have not been repeated in the context of current therapies for heart failure, such as the availability of metolazone to facilitate resolution of volume overload. This rate of clinical improvement is similar to that observed with the vasodilator nesiritide.46 The recent randomized trials have demonstrated, however, the high rate of clinical improvement perceived by both physicians and patients during routine diuretic therapy alone regardless of concomitant intravenous infusions.28,35

Recent information raises suspicion but does not prove that there may be deleterious effects over the longer term from a brief inotropic infusion in the hospital. There was a trend for worse outcome at 6 months after an in-hospital infusion of dobutamine compared with outcomes after nesiritide.29 A delayed impact of brief infusions was also suggested by a trial that showed higher 6-month mortality after 24-hour infusion with dobutamine than with the calcium sensitizer levosimendan.47 Possible mechanisms for such an effect include delayed effects of in-hospital events such as tachyarrhythmias or subclinical myocardial ischemia and apoptosis as a result of increased sympathetic stimulation and intramyocardial calcium accumulation. A recent retrospective analysis has also raised the question of whether nesiritide increases mortality more than placebo infusions, leaving open the question of when any vasoactive infusion should be added to facilitate diuresis in the absence of complicating hypoperfusion or renal dysfunction. Design of therapy for patients hospitalized with heart failure will be facilitated when better information is available regarding the targets at which therapy should be aimed.

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