Therapy with intravenous inotropic agents is most often initiated as short-term therapy during hospitalization to achieve one of several goals for acute management of decompensation, as described in part I of this report (Table). However, it may become difficult to wean these infusions in some patients as a heart failure progresses to late stages.

**Chronic Inotropic Infusions as Bridging Therapy**

**Identification of Inotrope Dependence**

Many considered initially to be dependent on inotropic infusions can undergo successful weaning after complete diuresis of excess volume and careful adjustment of concomitant oral medications, which may be facilitated by hemodynamic monitoring to optimize loading conditions on oral agents. β-Adrenergic receptor antagonists would have been discontinued already in most cases. ACE inhibitors may need to be discontinued to maximize blood pressure and renal function, with addition of nitrates with or without hydralazine as needed for vasodilation. Dependence should not be declared until multiple interventions and weaning attempts have been made, in most cases requiring 2 to 3 weeks in the hospital, a systematic approach discussed by Hershberger et al.

Although its magnitude can be debated, there is clearly a population of patients who are considered by experienced heart failure teams to be dependent on intravenous inotropic infusions despite multiple weaning attempts. It is assumed that such patients would not survive hospital discharge without ongoing inotropic support, although consensus has not been reached on exactly who they are. Dependence is most often manifested as symptomatic hypotension, recurrent congestive symptoms, or worsening renal function early after discontinuation of inotropic therapy. It should be emphasized that dependence for clinical purposes should be defined by limited clinical function, not by measured hemodynamic parameters, although these numbers have been required for Medicare coverage of home infusions in some states. For patients considered dependent, continuous inotropic therapy is then used to serve as a “bridge” to arrival at a destination such as transplantation or the end of life.

Prolonged use requires insertion of an indwelling intravenous line, usually linked to a wearable drug-infusion pump. Before the catheter is inserted, it is critical to ascertain the adequacy of community home health agencies to help maintain the access site and pump and the understanding of the patient and family as to its function and ultimate purpose. Maintenance of chronic intravenous infusions is associated with numerous infectious and mechanical complications from the infusion catheter in addition to those related to the drug.

**Bridge to Transplant**

The most common indication for bridging therapy is to provide hemodynamic support until a suitable donor heart becomes available for cardiac transplantation. Candidates in whom an inotropic infusion has become necessary frequently progress to higher doses, then combinations of dobutamine with milrinone. As the number of waiting candidates increases, some patients who appear to be stable on intravenous inotropic infusions have been sent home to wait, usually with implantable defibrillators in place. Such patients frequently require rehospitalization because of progressive hemodynamic instability but can occasionally improve to be weaned from inotropic support while still at home before transplantation. As waiting times on intravenous inotropic therapy lengthen, often to many months, it is increasingly recognized that organ function and nutritional status frequently continue to decline on this therapy. In some cases, an accelerated decline may result if eosinophilic myocarditis develops as an allergic response to the dobutamine. This is most often identified on examination of the explanted heart, but surveillance of peripheral eosinophil counts may identify most such patients. For transplant candidates dependent on inotropic infusions, ventricular assist devices are being considered earlier, particularly as indices of nutrition decline.

**Survival With Outpatient Inotropic Therapy**

When heart failure has progressed to the stage at which outpatient inotropic infusions are considered, survival is severely limited if heart transplantation is not an option. It cannot easily be resolved whether the use of inotropic therapy...
Chronic therapy “until
Intermittent outpatient therapy
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.24 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
Resolution of congestion with impaired renal responses
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.20 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.

Figure 1. Mortality estimated from selection of experiences with intravenous inotropic (ino) therapy. Mortality in intravenous inotropic trials from controlled experiences is shown in shaded triangles, with placebo mortality in open triangles.16–19 Circles represent uncontrolled experiences.5–7,13,14,35,36 Where available, actuarial mortality is presented. Otherwise, time shown on x-axis is median follow-up. For comparison, mortality with oral milrinone for class IV patients in combination with ACE inhibitors, digoxin, and diuretics is indicated by open square.25 Patients specifically determined to be dependent on inotropic infusions in experience of University of Oregon are shown at 6 and 12 months by solid squares.23 Mortality for patients considered dependent on inotropic infusions (Ino dep) in control arm of REMATCH trial of left ventricular assist devices as destination therapy23 is shown with closed diamonds.

hospitalization of 3 weeks.3 In the Randomized Evaluation of Mechanical Assistance in Congestive Heart Failure (REMATCH) trial,9 50% of the trial population had been deemed inotropic dependent at the time of randomization by having failed 2 weaning attempts under the supervision of cardiologists specifically certified for heart failure clinical practice and clinical trial experience. Because these patients received intense supervision without other therapeutic option, they provide a benchmark of the characteristics and outcome of inotropic infusions in end-stage heart failure (Figure 1), with 61% mortality at 6 months and 79% mortality by 1 year.

Bridging to the End of Life
With the high mortality on chronic inotropic infusions when transplantation is not an option, it should be considered a terminal therapy. The use of continuous outpatient inotropic infusions at the end of life is increasing, even at heart failure centers previously opposed to the practice. This reflects an evolving population who survive long enough to develop refractory symptoms. Chronic therapy with neurohormonal antagonists has reduced the incidence of sudden death, whereas progression of heart failure is delayed but not halted. The prevalence of implantable defibrillators further decreases the chance that death will occur before or during unremitting symptoms of circulatory decompensation. Our forward progress has driven us to desperation, where we reach back for the inotropic therapies that we learned to fear in the past. As our connections with patients span more years, we have had the opportunity to become more personally involved with them and their families through their journey and to respond personally to their desperation as the end approaches. It is difficult to withhold a therapy that recently restored comfort. In a recent survey of 71 US heart failure programs, more than 95% of the responding physicians indicated willingness to use outpatient inotropic infusions, although 80% had seen

Support until resolution of other conditions
Recovery from sustained tachyarrhythmia or infarction
Recovery from noncardiac surgery

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.24 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
Resolution of congestion with impaired renal responses
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.20 Other trials feasible in different patient cohorts.
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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.

From collected experiences, the anticipated mortality rate at 6 months is more than 50%, and few survivors will remain at 1 year (Figure 1). Survival is the worst in a recent series of patients in whom inotropic dependence was defined prospectively after specific weaning attempts. In this experience from the University of Oregon, mortality was 94% at 1 year for 36 patients who failed multiple weaning attempts during a mean of 11 weeks. The prevalence of implantable defibrillators further decreases the chance that death will occur before or during unremitting symptoms of circulatory decompensation. Our forward progress has driven us to desperation, where we reach back for the inotropic therapies that we learned to fear in the past. As our connections with patients span more years, we have had the opportunity to become more personally involved with them and their families through their journey and to respond personally to their desperation as the end approaches. It is difficult to withhold a therapy that recently restored comfort. In a recent survey of 71 US heart failure programs, more than 95% of the responding physicians indicated willingness to use outpatient inotropic infusions, although 80% had seen
worsening heart failure, 69% had seen infectious complications, and 50% had seen sudden death during such infusions (J.B. Young, MD, Cleveland Clinic, and L.W. Miller, University of Minnesota, written communication, 1994). This consensus is reflected in the latest version of the American College of Cardiology/American Heart Association guidelines for heart failure.10

What do these inotropic therapies achieve? Prolonged survival is certainly not the goal (Figure 1). Are patients dying comfortably at home? The majority of patients are rehospitalized at least once, with a small number undergoing multiple rehospitalizations, to die eventually in the hospital.3 Many patients are able to die out of the hospital, which is desired by them and families. Some, however, are not able to endure the final vigil at home. This may be eased when the current hospice criteria more uniformly accept the use of intravenous inotropic agents for comfort and can provide other end-of-life support in the home. Alternatively, the judicious use of narcotics and anxiolytics may provide similar comfort for some patients without the need for intravenous catheters.

**Intermittent Infusions for Outpatients**

On the basis of the inpatient experiences, inotropic infusions have also been administered intermittently at home or at outpatient infusion clinics on a regular schedule.5,11–13 Improvement in symptoms and reduction in rehospitalization have been demonstrated for some patients after enrollment in these programs. Other experiences in patients with more severe compromise have shown high early mortality (80% at 6 months in one study), without obvious clinical benefit.14 In the broader context of heart failure disease management, patients enrolled in such programs also receive extensive patient education, frequent phone contact, and regular clinical assessment, which have been shown to improve heart failure outcomes. The reimbursement for outpatient infusion clinics may have helped to support more staff to provide this vital education and ongoing personal connection that is otherwise not supported outside of research. It is unclear whether there is an additional benefit of the intermittent inotropic infusions that would outweigh the risks of increased ventricular tachycardia15 and ischemia during and after administration. Of 4 small randomized studies, 2 showed higher mortality with the use of intermittent infusions.16,17 A randomized study of hemodynamics after 1 month of dobutamine or placebo infusion showed the only significant difference to be a 2-kg weight loss compared with 1 kg in the placebo group, attributed to enhanced diuresis.18 A more recent randomized trial, which included 38 New York Heart Association functional class III or IV patients receiving 2.5 µg·kg⁻¹·min⁻¹ of dobutamine for 48 hours weekly over 6 months, showed no improvement in clinical class or 6-minute walk distance.19 Much of the outpatient infusion experience has been with dobutamine, although there has been some experience with amrinone and milrinone.11,13 A randomized trial of intermittent outpatient infusions of milrinone, referred to as the ROME trial, was apparently terminated after ~100 patients were enrolled, but no information has yet become available regarding the results. Unless these data indicated benefit, the negative results of the inpatient OPTIME trial (Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure) of 48-hour infusions might also be extrapolated to indicate a low likelihood of benefit from shorter milrinone infusions for routine management of outpatients with heart failure.20

**Future of Inotropic Therapy**

**“New” Inotropic Drugs**

It is estimated that more than 100,000 patients with heart failure characterized by ventricular dilation and reduced ejection fraction currently have chronic symptoms at rest or with minimal exertion even with access to the best medical therapy currently available in the United States.21 Human heart transplantation or implantation of a left ventricular assist device are options for highly selected patients but are unlikely to be available for the majority. These patients and their families continue to be drawn by the hope of relief. Although patients with heart failure rarely wish to forego resuscitation,22 most of those with New York Heart Association functional class IV heart failure indicated willingness to trade at least half of their remaining time or accept at least 50% risk of death to receive therapy that restores better quality of life.23 The new legitimacy of palliation for heart failure is acknowledged in the latest American College of Cardiology/American Heart Association guidelines for the management of chronic heart failure.10 The desperate desire for such therapy is underlined by the acceptance by physicians, patients, and families of the added risk of complications from chronic indwelling catheters for outpatient inotropic therapy with drugs known to increase mortality in less severe disease. It is ironic that these infusions are available, whereas the oral medication vesnarinone was halted in development despite improved symptoms for at least 16 weeks, with an absolute increase in risk of death <5% yearly.24 Unlike the previous experience with chronic milrinone,25 there was no increase in hospitalizations or in deaths attributed to heart failure with vesnarinone. We may now be willing to consider new oral agents with potential symptomatic benefit even if risks are similar to those of previously abandoned drugs. In addition, the increasing prevalence of implantable defibrillators may alter the relative risk of sudden death during chronic therapy with oral inotropic agents. Although there are multiple intravenous agents available for brief therapy during heart failure hospitalization, the demand is for new inotropic therapy for chronic oral administration, a demand created by this extending population and those who care for them. Development of a new intravenous agent would be welcomed if it offered smooth transition to a chronic oral form.

The currently available inotropic therapies stimulate cAMP and increase intracellular calcium levels either through β-adrenergic receptor stimulation or through phosphodiesterase inhibition as part of their primary mode of action. Increased cytosolic calcium contributes to altered gene expression and apoptosis and increases the chance of ventricular arrhythmias (Figure 2).
The calcium sensitizers, exemplified by levosimendan, increase the sensitivity of troponin C to calcium in relation to calcium concentration. This allows improved contractility without increased intracellular calcium or compromise of diastolic relaxation. Short-term administration improves cardiac output and lowers filling pressures acutely, with small increases in heart rate. The oral formulation, which required adjustment for a long-acting metabolite, allowed frequent weaning of intravenous inotropic infusions in a pilot trial that has not yet been expanded. The intravenous form led to greater hemodynamic improvement than dobutamine at the end of 24-hour infusion, with a trend toward lower mortality at 6 months.29

**Targeted Gene Expression**

Elucidation of the molecular mechanisms involved in calcium regulation within the myocyte is revealing new targets for therapy to improve contractility, as reviewed recently.30

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**Figure 2.** Effects of inotropic therapy on intracellular calcium handling in cardiac myocytes. Depolarization of membrane by action potential leads to opening of voltage-gated L-type calcium (Ca\(^{2+}\)) channels, which allows entry of small amount of Ca\(^{2+}\) into cell. Through coupling mechanism between L-type Ca\(^{2+}\) channel and sarcoplasmic reticulum (SR) release channels (ryanodine receptors), larger amount of Ca\(^{2+}\) is released, which activates myofilaments, leading to contraction. During relaxation, Ca\(^{2+}\) is accumulated back into SR by SR Ca\(^{2+}\) ATPase pump (SERCA2a) and extruded extracellularly by sarcolemmal Na\(^+\)/Ca\(^{2+}\) exchanger. Many sarcolemmal receptors affect calcium handling in cardiac myocytes. Agonists through G proteins increase adenylyl cyclase (AC) activity, which results in cAMP production. This results in activation of protein kinase A (PKA), which leads to phosphorylation of L-type calcium channels, allowing increase in calcium entry, phosphorylation of phospholamban, increasing SERCA2a activity, and phosphorylation of troponin I, which decreases sensitivity of myofilaments to Ca\(^{2+}\). Phosphorylation effects of PKA induce greater release of calcium from SR and faster relaxation. Digoxin inhibits Na\(^+\)/K\(^+\) ATPase pump, which increases intracellular Na\(^+\). This results in increase in intracellular Ca\(^{2+}\) via Na\(^+\)/Ca\(^{2+}\) exchanger, which leads to enhanced Ca\(^{2+}\) loading of SR and increase in Ca\(^{2+}\) release. Phosphodiesterase inhibitors (PDEI) block breakdown of cAMP, which increases its intracellular level and activates PKA. Calcium sensitizers increase sensitivity of myofilaments to Ca\(^{2+}\), enhancing myoflament activation for any concentration of Ca\(^{2+}\). Vesnarinone prolongs action potential duration through modulation of K\(^+\) channels, thereby prolonging opening of L-type calcium channels and increasing Ca\(^{2+}\) entry. Through gene transfer of SERCA2a, modified phospholamban (mPL), or antisense phospholamban (asPL), SR ATPase activity can be increased, which enhances SR Ca\(^{2+}\) content, inotropic and lusitropic state. At level of cardiomyocyte, several stimuli, including endothelin-1 (ET-1), phenylephrine, and angiotensin, are involved in development of hypertrophy through Gq-coupled receptors. They induce activation of phospholipase C (PLC) and diacylglycerol (DAG), which increases levels of inositol triphosphate (IP3). IP3 induces release of calcium from SR. Increased cytosolic calcium induces mitogen-activated protein kinases (MAPK) and activates calcineurin and caspasas that contribute to apoptosis. Ang II indicates angiotensin II; NE, norepinephrine; PDE, phosphodiesterase; and PKC, protein kinase C. (Figure developed in collaboration with Roger Hajjar, MD, Cardiovascular Division, Massachusetts General Hospital, Boston, Mass.)
Impaired calcium uptake and release through the sarcoplasmic reticulum diminish systolic calcium release and the force of contraction and elevate diastolic calcium levels and filling pressures (Figure 2). The increasing efficiency of gene-transfer techniques has allowed demonstration of improved contractility and survival after viral transfection of the sarcoplasmic reticulum calcium ATPase (SERCA-2) into small animal models, and more recently in the swine model. Similar findings have been obtained with use of a phospholamban mutant that does not constrain SERCA-2 activity and an adenovirus that encodes antisense of phospholamban.

In each approach, improvement was seen in both inotropic and lusitropic performance. Furthermore, the acute hemodynamic benefits were associated with prolonged survival of the animal models. Therapy directed to improve calcium cycling addresses both the systolic and diastolic components of dysfunction (Figure 2).

Beyond calcium regulation, other major targets may be identified for intervention, such as increasing the proportion of the more powerful α-myosin heavy chains that are diminished in heart failure. It is not yet known with what feasibility targeted gene approaches can be translated to human heart failure with catheter-based and surgical techniques. They may also represent one of the strategies through which functional myocardial improvement may be achieved as the heart rests during mechanical unloading with assist devices.

Looking Backward and Forward

Therapy with inotropic agents evolved through the enthusiasm of increased contractility and disappointment of increased mortality for chronic heart failure. Paradoxically, the success of current neurohormonal therapies and implantable defibrillators has created a population of survivors with less chance of sudden death who now require increasing hospitalizations as the disease approaches its end. Right ventricular failure and cardiorenal interactions further limit the efficacy of currently recommended therapy. For most patients with comorbidities and advancing age, transplantation and current devices are mirages that intensify the desire for something better. Although the heaviest symptom burden is that of congestion, the backward failure, improvement of contractility and forward perfusion is sometimes the only direct route to relief. After the abandonment of previous oral inotropic agents with modest decrement in survival, chronic inotropic therapy is now offered in a more morbid form, as catheter infusion “until” something else happens, usually death. Looking forward, it remains to be revealed how far we will advance beyond draining congestive symptoms and squeezing forward flow to restore myocyte function and circulatory integration.

References


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