Chronic Inotropic Therapy in the Current Era
Old Wines With New Pairings

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In the current issue of Circulation: Heart Failure, Hashim and fellow researchers from the University of Alabama at Birmingham have published their outcomes for advanced heart failure (HF) patients supported with chronic inotropic infusions for a variety of indications, including bridging to transplantation, anticipation of left ventricular assist device (LVAD) placement or for palliation.1 This single-center retrospective series of 197 patients describes better patient survival than most previous reports, with a median survival of 18 months compared with 3 to 6 months.2–4 Median survival was 9 months for those patients in whom continuous inotropic therapy was intended solely as palliation, with a 1-year actuarial survival of 48% and a 2-year actuarial survival of 38%. Filling pressures and cardiac index improved, and subjective symptom class decreased from Class IV at baseline to median Class III after discharge.

Improving Chances for 1-Year Survival

Intravenous inotropic therapy has been described as the “until therapy.”2 Patients with Stage D HF may be discharged on this therapy with the intention of use until cardiac transplantation or determination of transplant eligibility and can also be used until decision or implementation of mechanical circulatory support. Outcomes of inotropic therapy for these patients are highly influenced by regional transplant waiting times and more recently by the threshold for implantation of ventricular assist devices. The focus of this editorial will instead be the outcomes and options for those patients discharged on inotropic therapy intended as the last specific intervention to improve symptoms of HF until the end.

What accounts for the apparent improvement in survival in this report? These clinicians experienced in triage of Class D patients studied an appropriate HF population similar to experiences previously summarized with median survival of ≈6 months on chronic inotropic therapy.2,4 There were multiple previous hospitalizations, and the mean ejection fraction was 18%; cardiac index, 1.7 L/min per m²; pulmonary capillary wedge pressure, 26 mm Hg; and cardiac index, 1.9 L/min per m². In the most detailed report from the previous era, Hershberger in 20034 described a 1-year survival of only 6% in patients with similarly severe compromise and no option for transplantation, with cardiac index of 1.9 L/min per m² and pulmonary capillary wedge pressure of 28 mm Hg, although he documented more rigorous criteria for failed weaning.

Could the improved survival in this report result from the high rate of continuation of neurohormonal antagonists, particularly the 72% for β-blockers? This seems unlikely because another recent report of continuous inotropic therapy by Gorodeski from the Cleveland Clinic showed a similar 1-year survival of ≈50% on milrinone with only 19% baseline use of β-blockers.5 An attractive case has been made for the combination.6 A related hypothesis was tested in the Studies of Oral Enoximone Therapy in Advanced HF (ESSENTIAL) program, which combined a low dose of the oral PDE-3 inhibitor, enoximone, with β-blockers.7 This combination produced variable improvements in 6-minute walk distance, but failed to improve survival or improve patient well-being.

One important aspect of inotropic therapy and survival may relate to intensity of dosing. Increasing familiarity with inotropic therapy to support diuresis during acute decompensated HF has led to the use of lower doses. The current trial reported median doses of 4.4 μg/kg per minute for dobutamine and 0.3 μg/kg per minute for milrinone, which was similar to the 5.4 μg/kg per minute for dobutamine and 0.4 μg/kg per minute for milrinone in the Gorodeski report.5 This contrasts to the Hershberger experience from 2003, in which the doses of dobutamine were 7 to 10 μg/kg per minute; dopamine, 5 μg/kg; and milrinone, 0.6 μg/kg per minute.4

Better recent survival seems most likely to reflect the greater prevalence of implantable cardioverter defibrillators (ICDs) in both this study and the Gorodeski report, in which 67% had implanted defibrillators.8 In the current study, only 11 of the 113 patients receiving inotropes for palliation were discharged home without some form of defibrillator. After discharge, 33 patients (17%) received at least one defibrillator shock with a mean of 3.3 shocks, although neither the shocked rhythms nor the lengths of survival after shock were described. The excess mortality seen in the past with the oral inotropic agent vesnarinone trial was attributed solely to an increase in death occurring suddenly.4 Ventricular tachyarrhythmias on inotropic therapy in the current era may have been successfully treated by antitachycardia pacing or defibrillation. Sudden death in advanced HF can also be caused by bradycardiac rhythms, which in some cases may be corrected by back-up device pacing. During overall follow-up in this study, there
was no systematic tracking of ICD settings, but 19 patients were known to have had their ICDs inactivated.

Stage D: Dining in a Data-Free Country
Stage D HF has been defined as advanced HF with continued HF symptoms requiring aggressive medical therapy.9 Class IV symptoms, occurring at rest or with minimal exertion, are assumed to be present in the absence of one of the therapies specifically indicated to treat patients at this stage. Patients with Stage D HF are not represented in randomized trials of medical therapies or arrhythmia devices, and there are only a few hundred patients in randomized trials of ventricular assist devices. All other recommendations for Stage D HF are based on consensus opinion, and some clinical decisions are not addressed at all.

The Medical Menu
Chronic inotropic therapy has been investigated in many early clinical studies in HF when it was considered to be a disease of impaired contractility and reduced cardiac output. Repeated disappointments shifted the focus of intervention away from oral inotropic agents because they were consistently shown to increase mortality and, in some cases, also to accelerate disease progression, despite initial hemodynamic and symptomatic improvement.10 Although an increase in sudden death led to an increase in overall mortality with vesiﬁnarinone as well, it was associated with significant improvements in quality of life that were evident at 2 and 4 months in Stage IV patients, although no longer evident by 6 months.11 Based on these experiences, the use of chronic inotropic therapy is often regarded as a choice to be made as to whether improvement in quality of life is worth the cost of shortened survival. However, it is not known whether inotropic therapy actually worsens survival compared with the limited other medical options for patients who have true Stage D resting hemodynamic decompensation. The randomized trials of oral inotropic therapy have studied only Stage C patients. Even within Class C, Class III patients were 58% of the primary oral milrinone study and 85% of the study population of the final vesinarinone study. Neurohormonal antagonists have become the cornerstones of therapy for HF. Adverse cardiac remodeling related to abnormal wall stress and neurohormonal activation is a primary determinant of HF survival.12 Therapies that antagonize the chronically deleterious effects of angiotensin II and norepinephrine have markedly ameliorated the remodeling process, decreased clinical disease progression, and consistently improved HF patient survival.13 Further restoration of geometry and functional and survival benefit has been seen with cardiac resynchronization therapy. Neurohormonal antagonism with angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker, β-blockers, and mineralocorticoid antagonists with careful monitoring is the key to therapy for Stage B and C HF,9 for which the outlook has improved dramatically as a result of these therapies and further with the systematic intervention to improve adherence to these guideline recommendations.

However, some patients progress to Stage D HF, despite appropriate use of all recommended medical and device therapies. The role of neurohormonal antagonists for Stage D HF has not been demonstrated. It is not clear to what degree the renin–angiotensin and the sympathetic nervous systems may help to support the circulation as contractility, renal perfusion, and diuretic responses diminish. Poor prognosis is well recognized when patients who previously tolerated angiotensin-converting enzyme inhibitor have them discontinued for symptomatic hypotension or renal dysfunction that limits decongestion.14 Patients whose β-blocker doses have to be decreased or stopped clearly have worse outcomes than those in whom β-blockers can be continued.15

Inotropic Therapy and Neurohormonal Antagonists?
This trial and the recent report from Cleveland Clinic1,5 both report at least half of patients remaining on angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker at initiation of chronic inotropic therapy. The use of β-blocker therapy at time of inotropic therapy differs, used in 80% of patients in the current Alabama study and 19% in the Cleveland study. A fundamental question arises: is it better to stop neurohormonal antagonists if necessary to avoid the risk of inotropic therapy, or is it better to continue neurohormonal antagonism even if it necessitates inotropic hemodynamic support to maintain adequate blood pressure and renal function? Effective renal autoregulation requires adequate blood pressure, which has been cited as a mean arterial pressure of 80 mmHg.16 Without a strong basis of evidence, how should we assess the thresholds for acceptable blood pressure and renal function in individual patients?

Similar questions pertain to attempts to wean inotropic therapy. The current study describes 24 patients weaned from inotropic therapy, with 68 dying and 50 remaining on inotropic therapy if not receiving transplant or LVAD therapy. How should neurohormonal antagonist therapy be adjusted during inotropic weaning? Is it better to remain on both neurohormonal antagonist and inotropic therapy than to be on neither? There is no basis of evidence on which to make these decisions. A recent review suggested that patients receiving intravenous inotropic therapy during hospitalization for acute decompensated HF had better outcomes if β-blocker therapy was maintained.13 This provides some reassurance regarding the acute combination, but shares the bias with other nonrandomized reports that patients tolerating neurohormonal antagonists generally have better hemodynamic compensation than those patients in whom they are withdrawn.

Sharing Decisions With Patients
A recent consensus statement from the Heart Failure Society of America recommends that several criteria be fulfilled before discharging patients on home inotropic therapy.17 Among these are a clear demonstration of symptomatic and hemodynamic improvement; optimization of neurohormonal antagonists and diuretics; failed weaning attempts; a determination that a patient is not a candidate for or has no desire for an LVAD or heart transplant; and, importantly, that there has been a detailed discussion of patient goals recognizing that the inotrope may fail to improve, and may worsen, survival.

Continuous Inotropic Therapy Versus Destination LVAD
The majority of patients with Stage D HF are ineligible for LVAD therapy, most commonly because of right HF;
noncardiac comorbidities, and general frailty. However, for those Stage D patients who are eligible, this is one of the few situations where some individuals might choose continuous inotropic therapy as more consistent with their preferred quality of life, even though better survival has actually been demonstrated with an alternative therapy. One-year mortality with destination LVADs is now about half the mortality demonstrated by the current study on continuous inotropic therapy. Data as provided in the current study facilitate development of tools for shared decision-making, which is the subject of ongoing research for the selected patients with this option.

Home Inotropic Infusion or Generic Palliation Alone?
For most patients, the decision is whether home inotropic infusion should be added to the more generic palliative regimen designed to help relieve the symptoms shared with other end-stage diseases. Discharge on continuous inotropic therapy for palliation should only be considered when it does establish reasonable hemodynamic and clinical stability in hospital, generally to allow independent ambulation and self care. After frank discussions regarding the limited and likely diminishing impact of this therapy, including the complications of indwelling intravenous catheters at home, the majority of patients who have family support generally choose to continue. It is vital that this choice not be dictated by arbitrary restrictions of hospice agencies. Fortunately, palliative inotropic infusion and potential weaning of these infusions at home have become increasingly accepted by hospice and bridge to hospice agencies.

However, limited resources at home or in the community sometimes still preclude discharge with infusions, which then have to be weaned in hospital, usually with accelerated titration of narcotics and other medications to palliate end-stage symptoms, such as anxiety and sleeplessness. Experience has taught us the necessity of designing a plan for discharge of these patients even when it seems medically unlikely that they will survive weaning. If patients are sustained by an intense desire to return home before death, it is surprising how often they can survive in comfort without inotropes not only for the ride but also for a meaningful few days at home with their families.

Continuous Inotropic Therapy for Palliation With Defibrillation?
The presence of ICDs may have contributed to the improved survival in this study compared with previous experiences with continuous inotropic therapy. For the majority of Stage D patients in the United States, ICDs have previously been implanted. Particularly when considering chronic inotropic therapy, formal discussion should take place with patients regarding inactivation of defibrillation, which may be most relevant for patients who have previously experienced shocks. The current Alabama report described at least 19 patients whose devices were inactivated. Decisions regarding ICD generator changes for patients without chronic pacing should also be carefully considered.

Occasionally, a rapid progression of HF may lead to dependence on intravenous inotropic infusions for a patient without a prior ICD. The pivotal ICD trials excluded patients with Class IV symptoms and did not show benefit of ICDs until after the first year. Although sudden death may occur sooner in Stage D patients, the majority of deaths are caused by progression of hemodynamic decompensation. The horizon of cost-effectiveness for ICD implantation does not support the implantation of an ICD in patients on continuous inotropic therapy as palliation for Stage D HF, except in potential transplant candidates. The LifeVest as used in a few patients in the current study may present a reasonable option for those patients who remain anxious to prevent sudden death, and it can conveniently be discontinued when it interferes with desired comfort.

Does Continuous Inotropic Therapy Have to Be Intravenous?
This study confirms the continuing need for additional therapies to improve hemodynamics and function for Stage D HF, with or without improvements in survival. Recent investigation suggests that calcium cycling and intracellular signaling pathways may be modulated to produce increased inotropy and lusitropy without increasing arrhythmogenesis, apoptosis, or direct cellular toxicity. Unless or until such therapies are available, continuous intravenous inotropic therapy will frequently be considered for Stage D patients. It is unfortunate that these patients must also accept the additional discomforts, inconvenience, and risks of the indwelling intravenous catheter when similar oral therapies have been developed. Individual preferences for quality of life are increasingly recognized. However, approval of oral inotropic therapies would require robust demonstration of patient-reported quality-of-life outcomes in randomized trials large enough to establish a relevant range of possible mortality risk. Concern has been expressed that availability of oral inotropic therapy to improve symptoms and function for this population might lead to irresponsible use in Stage C patients. That may be giving too little credit to clinicians who have as a community shown remarkably effective quality improvement in use of other recommended therapies for HF. On the contrary, ongoing progress in developing decision aids for life-threatening disease may empower eligible patients to choose their own therapies to enhance their own lives.

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References


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