Clinical Characteristics and Outcomes of Intravenous Inotropic Therapy in Advanced Heart Failure

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Background—Inotrope use in heart failure treatment was associated with improved symptoms, but worse survival in clinical trials. However, these studies predated use of modern heart failure therapies. This study evaluates contemporary outcomes on long-term inotropes.

Methods and Results—We collected baseline and postinotrope data on 197 patients discharged on inotropes between January 2007 and March 2013. Baseline characteristics, hemodynamic and clinical changes on inotropes, and survival were evaluated. Patients initiated on inotropes had refractory heart failure, with median baseline New York Heart Association class IV, cardiac index of 1.7 L/min per m², pulmonary capillary wedge pressure of 25.6 mm Hg, and left ventricular ejection fraction of 18.7%. Inotropes were used in patients listed for transplant or scheduled for LVAD. At the end of the study, 68 patients had died, 24 were weaned off inotropes, 23 were transplanted, 32 received LVADs, and 50 remained on inotropes. Patients who received inotropes for palliation or those who preferred inotropes over LVAD had median survival of 9.0 months (interquartile range, 3.1–37.1 months), actuarial 1-year survival of 47.6%, and 2-year survival of 38.4%. Of 60 patients who were placed on inotropes as a bridge to transplant/LVAD, 55 were successfully maintained on inotropes until transplant/LVAD.

Conclusions—Survival on inotropes for patients who are not candidates for transplant/LVAD is modestly better than previously reported, but remains poor. Inotropes are effective as a bridge to transplant/LVAD. (Circ Heart Fail. 2015;8:880-886. DOI: 10.1161/CIRCHEARTFAILURE.114.001778.)

Key Words: dobutamine ■ heart failure ■ milrinone ■ quality of life ■ survival

Approximately 6 million adults currently have heart failure (HF) in the United States, and this is expected to increase to 8.4 million by 2030. The number of patients with advanced HF who have refractory symptoms, despite medical therapy, is also expected to increase. Options for the majority of these patients with end-stage heart disease are limited. Both heart transplantation and mechanical circulatory support improve survival and quality of life, but because of limited donor supply and medical comorbidities, most patients are not candidates for these life-saving therapies. The 1-year survival in the medical management group of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, which studied such patients, was dismal, at 25%. Inotropes are sometimes used in these patients, but despite evidence that they improve hemodynamics, continuous outpatient inotrope use has not been shown to improve survival, and in some cases has worsened survival, with studies reporting a 6-month mortality between 40% and 74%. However, many inotrope trials predated the use of modern HF therapies, including implantable cardioverter defibrillators (ICDs), cardiac resynchronization therapy, aldosterone antagonists, and even β-blockers in some cases. These therapies may have altered the prognosis of patients on chronic inotropes. The purpose of this study is to evaluate outcomes of patient with stage D HF on chronic outpatient support with inotropic therapy in a contemporary patient population.

Methods

This study was a retrospective review of all adult patients with advanced HF discharged from a single institution on continuous milrinone or dobutamine from January 2007 to March 2013. Patients on an inotrope were identified by several means: review of our patient records for that period for 3 of 5 home infusion companies.
Clinical Data and Outcomes

The primary outcome measure was all-cause mortality. Data were collected on participants until they died, received an LVAD or transplant, were weaned off inotropes, or remained on inotropes at the end of the data collection period. For patients who were weaned off inotropes, survival was assessed 1 year later. Vital status was ascertained using review of hospital data, clinic charts, infusion company records, and the Social Security Death Index. Functional status, physical examination, catheterization, echocardiographic data, and laboratory data were collected before initiation of inotropes and at the time of the first clinic or catheterization visit after being on inotropes. ICD interrogation and hospitalization data were collected throughout the follow-up period.

Statistical Analysis

Continuous variables are presented as mean±SD. Pre and postinotrope clinical echocardiographic, laboratory, and hemodynamic data were compared using paired t tests for continuous data, and χ² tests for categorical data. The Kaplan–Meier method was used to evaluate survival. Patients were censored at the time of transplant, LVAD, on the date that they were completely weaned off inotropes, or at the end of the study if they remained on inotropes. Statistical analysis was performed using Statistical Analysis Software (SAS) 9.3.

Results

Baseline Characteristics

We identified 197 consecutive patients who were discharged on continuous inotropes between January 2007 and March 2013. The median baseline New York Heart Association class was IV, mean age was 54.4 years (±14.6 years), 40% had ischemic cardiomyopathy, and 25.8% were women. At least 58% of patients had ≥2 hospitalizations for HF in the year before inotrope initiation. Milrinone was used in 84.8% of patients at a mean discharge dose of 0.296 (±0.092) μg/kg per minute, and dobutamine was used in 15.2% of patients at a mean dose of 4.38 (±1.78) μg/kg per minute. The baseline mean arterial pressure was 79.2 mm Hg in the milrinone group and 74.7 mm Hg in the dobutamine group (p 0.07). Almost 90% of patients were known to have ICD/CRT-D or a Lifevest (Table 1). Patients were placed on inotropes for several reasons: as a bridge in patients listed for transplant or scheduled for LVAD (60 patients), for patients being evaluated for LVAD/transplant (20 patients), for acute stabilization pending cardiac resynchronization therapy or high-risk percutaneous coronary intervention (4 patients), in patients who were offered LVAD evaluation but refused and preferred inotropes (15 patients), and for palliation (98 patients).

Clinical and Laboratory Data Pre- and Postinotrope

Baseline studies showed poor hemodynamics, with mean right atrial pressure of 14.8 (±7.0) mm Hg, pulmonary capillary wedge pressure of 25.6 (±8.1) mm Hg, and assumed Fick cardiac index of 1.7 (±0.4) L/min per m². The baseline left arterial pressure was 79.2 mm Hg in the milrinone group and 85.2 (±18.8) mm Hg in the dobutamine group (p 0.07). Almost 90% of patients were known to have ICD/CRT-D or a Lifevest.
ventricular ejection fraction was 18.7 (±8.1) %. After initiation of inotropes and discharge from the hospital, most patients were seen in clinic within 4 to 6 weeks (Table 2). At the time of the first postinotrope outpatient measurement, there was improvement in mean cardiac index to 2.2 (±0.5) L/min per m², decrease in pulmonary capillary wedge pressure to 21.1 (±9.0) mm Hg, and improvement in left ventricular ejection fraction to 21.1 (±10.1)%. Mean blood urea nitrogen level decreased from 31.1 (±20.2) to 26.6 (±19.9) mg/dL and mean serum creatinine improved from 1.6 (±0.8) to 1.5 (±0.7) mg/dL. There was also improvement in congestion as measured by weight and serum brain natriuretic peptide levels (Table 3). The median New York Heart Association class improved from IV to III. Patients who died and those who remained on inotropes had more hospitalizations than those who were weaned off, transplanted, or underwent LVAD placement (Table 2). Oral HF medications were maintained during inotrope therapy in a substantial proportion of patients (Table 4).

All the patients who were candidates for LVAD/transplant had ICDs or Lifesvest active until LVAD/transplant. Among the 113 patients who were not candidates for LVAD/transplant, 11 were discharged home on inotropes without ICD or Lifesvest. Nineteen additional patients had ICDs deactivated at our institution at a median of 190 days (interquartile range, 23–479) after inotrope initiation. Some patients may have had their ICDs deactivated at home by their hospice physicians, and this information was not available. During follow-up, 33 patients (16.7%) had ICD shocks. These patients had a mean of 2.09 (±1.8) episodes of shocks and 3.3 (±3.0) total ICD shocks.

Outcomes and Survival
Sixty-eight patients died, 24 were weaned off inotropes, 23 were transplanted, 32 received an LVAD, and 50 remained on inotropes at the end of the study. The subset of patients who were placed on inotropes for palliation or those who were offered LVAD but chose inotropes had median survival of 9.0 months (interquartile range, 3.1–37.1 months; Figure 1). The 1-year actuarial survival for this group was 47.6%, and the 2-year actuarial survival was 38.4%.

Fifty-five of the 60 patients (92%) who were placed on inotropes pending LVAD or transplant were successfully supported on inotropes until LVAD or transplant. Among all patients placed on inotropes, 24 were successfully weaned off, of whom 19 were alive, 3 had died, and 2 were lost to follow-up 1 year later. Clinical characteristics of patients weaned off inotropes are listed in Table 5. Among all patients placed on inotropes, those on milrinone had a better survival than those on dobutamine (log rank P = 0.01; Figure 2).
The management of patients with advanced HF can be challenging. They are often already on maximally tolerated oral therapy, hypotension precludes aggressive afterload reduction, and intensive diuretic therapy often worsens cardiorenal syndrome. Those who are not candidates for LV AD or transplant have poor outcomes.

Inotropes are often used for acute hemodynamic stabilization or until resolution of the condition that precipitated the acute decompensation or shock, but their role in chronic management is more complex. Studies of chronic inotrope use from the late 1980s to early 2000s showed poor outcomes, with 6-month mortality in excess of 50%. However, these previous studies differed considerably from modern practice in regard to patient selection and management. There are no recent trials on chronic inotropic use, and given the clinical uncertainty and controversy over their use, there is wide variation in inotrope use among institutions.

The 2 largest and most influential studies to examine inotrope therapy with currently available inotropes are Prospective Randomized Milrinone Survival Evaluation (PROMISE) and Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF). PROMISE enrolled 1088 patients with New York Heart Association III or IV HF between 1989 and 1990, and randomized them to placebo or oral milrinone. Patients did not have defibrillators, and those requiring β-blockers were excluded. The milrinone group had 28% higher mortality at 6.1 months. OPTIME-CHF evaluated in-hospital inotrope use in 958 patients with HF exacerbation between 1997 and 1999. The primary end point was the number of days hospitalized for cardiovascular causes within 60 days. Patients were excluded if the treating physician judged that intravenous inotropic therapy was essential. There was more hypotension and atrial arrhythmias in the milrinone group, and no difference in the primary outcome or survival.

Neither of these populations reflects current patients with advanced HF who are being considered for long-term inotropes. OPTIME-CHF did not evaluate home inotrope use and specifically excluded patients with low output states and evidence of end-organ hypoperfusion, precisely the population that in current practice may be inotrope dependent. PROMISE was performed in an era without contemporary HF therapy including β-blockers, aldosterone antagonists, defibrillators, or cardiac resynchronization, and used oral rather than intravenous milrinone. Moreover, neither study evaluated hemodynamics at enrollment or with therapy in detail.

Many other studies on inotropes have been performed, with mixed results. Vesnarinone, ibopamine, and xamoterol are not used because of higher mortality in trials, and enoximone was safe but did not meet efficacy end points. Secondary

### Table 4. Neurohormonal Antagonist Use Before and During Inotrope Use

<table>
<thead>
<tr>
<th>Antagonist</th>
<th>Preinotrope</th>
<th>Postinotrope</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-blocker</td>
<td>Yes 159 (80.7%)</td>
<td>142 (72.1%)</td>
</tr>
<tr>
<td>No</td>
<td>32 (16.2%)</td>
<td>42 (21.3%)</td>
</tr>
<tr>
<td>Missing</td>
<td>6 (3.0%)</td>
<td>13 (6.6%)</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>Yes 103 (52.3%)</td>
<td>98 (49.7%)</td>
</tr>
<tr>
<td>No</td>
<td>85 (43.1%)</td>
<td>85 (43.1%)</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (4.6%)</td>
<td>14 (7.1%)</td>
</tr>
<tr>
<td>ARB</td>
<td>Yes 24 (12.2%)</td>
<td>25 (12.7%)</td>
</tr>
<tr>
<td>No</td>
<td>164 (83.2%)</td>
<td>157 (79.7%)</td>
</tr>
<tr>
<td>Missing</td>
<td>9 (4.6%)</td>
<td>15 (7.6%)</td>
</tr>
<tr>
<td>Aldosterone antagonist</td>
<td>Yes 105 (53.3%)</td>
<td>116 (58.9)</td>
</tr>
<tr>
<td>No</td>
<td>85 (43.1%)</td>
<td>65 (33.0%)</td>
</tr>
<tr>
<td>Missing</td>
<td>7 (3.6%)</td>
<td>16 (8.1%)</td>
</tr>
</tbody>
</table>

ARB indicates angiotensin II receptor blocker; and ACE, angiotensin-converting enzyme.
candidates for heart transplant or LVAD had a median survival of 9 months. This survival is modestly better than reported in previous studies, and this may be related to advances in medical therapy and high usage of electrophysiological devices that can treat ventricular fibrillation/ventricular tachycardia. However, despite contemporary medical and device therapy, survival is still suboptimal, similar to that in patients with stage IIIb non-small cell lung cancer or stage III pancreatic cancer. Conversely, inotropes were effective in bridging patients who were candidates for advanced therapies, with 92% of patients successfully supported until LVAD or transplant. Patients on inotropes had early symptomatic benefit, accompanied by improvement in hemodynamic parameters. Interestingly, 12% of patients who presented with a low output state were stabilized with inotropes, which were subsequently weaned off as an outpatient after optimization of contemporary oral and device therapy. At least 79% of patients weaned off inotropes were alive 1 year later.

In our study, a significant proportion of patients on inotropes were also maintained on oral HF therapy, including β-blockers. There is limited evidence on how the addition of β-blockers to inotrope therapy affects symptoms and survival. The effects of dobutamine are attenuated in the presence of β-blockers, but phosphodiesterase inhibitors continue to have hemodynamic effects in the presence of β-blockade. Several small studies of β-blockers in combination with milrinone have shown that this combination is well tolerated, may improve hemodynamics compared with milrinone alone, and that it is feasible to use inotropes initially in patients presenting with severe HF, then initiate β-blockers and other oral HF therapies with subsequent wean of inotropes. In a post hoc analysis of the OPTIME study, in patients who were continued on β-blockers on admission, there was no difference in the primary end point regardless of assignment to milrinone or placebo. Patients whose β-blockers were withdrawn on randomization to milrinone had worse outcomes. It has been our practice to use milrinone preferentially, attempt low dose β-blockers in patients on milrinone, and assess the feasibility of weaning inotropes in clinic visits.

Previous studies have not shown a consistent difference in survival between patients receiving milrinone and those receiving dobutamine. In this study, patients on milrinone had higher survival than those on dobutamine. However, given the small number of patients on dobutamine and potential differences in patient selection and characteristics that could have influenced outcomes, we are unable to make a robust claim about the independent effect of milrinone versus dobutamine on survival. We also used lower doses of milrinone than were reported in previous studies, which may have mitigated some of the arrhythmic and ischemic risks of milrinone.

Limitations of this study include the single-center nature of the study, which may reflect local practice patterns. Nevertheless, patients had objective clinical and hemodynamic evidence of advanced HF, with the severity of echocardiographic and hemodynamic abnormalities similar to that reported in other inotrope and LVAD studies, and were clinically inotrope dependent. There was incomplete clinical and hemodynamic data, but the primary outcome information was available on all patients. Identification of eligible patients may have been incomplete because of stepwise electronic medical record roll-out during the study period and lack of access to records from

Table 5. Demographic and Baseline Data for Subjects Who Were Weaned Off Inotropes

<table>
<thead>
<tr>
<th>Sex</th>
<th>N</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>9</td>
<td>37.5%</td>
</tr>
<tr>
<td>Men</td>
<td>15</td>
<td>62.5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of hospitalizations in a year before inotrope initiation</th>
<th>Unknown</th>
<th>5 (20.8%)</th>
<th>0</th>
<th>2 (8.3%)</th>
<th>1</th>
<th>7 (29.2%)</th>
<th>2</th>
<th>6 (25.0%)</th>
<th>3</th>
<th>4 (16.7%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Electrophysiology device</th>
<th>None</th>
<th>2 (8.3%)</th>
<th>ICD</th>
<th>10 (41.7%)</th>
<th>BIV-ICD</th>
<th>12 (50.0%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dobutamine</th>
<th>6 (25.0%)</th>
<th>Milrinone</th>
<th>18 (75.0%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>History of cardiac arrest</th>
<th>No</th>
<th>22 (91.7%)</th>
<th>Yes</th>
<th>2 (8.3%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Cause</th>
<th>Ischemic</th>
<th>8 (33.3%)</th>
<th>Nonischemic</th>
<th>16 (66.7%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Previous PCI</th>
<th>No</th>
<th>15 (62.5%)</th>
<th>Yes</th>
<th>9 (37.5%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Previous CABG</th>
<th>No</th>
<th>16 (66.7%)</th>
<th>Yes</th>
<th>8 (33.3%)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Ventricular tachycardia</th>
<th>No</th>
<th>19 (79.2%)</th>
<th>Yes</th>
<th>5 (20.8%)</th>
</tr>
</thead>
</table>

BW indicates biventricular; CABG, coronary artery bypass grafting; ICD, implantable cardioverter defibrillator; and PCI, percutaneous coronary intervention.

In light of the existing evidence, the 2013 guidelines from American College of Cardiology/American Heart Association recommend temporary intravenous inotropes for patients with cardiogenic shock until definite therapy or resolution of the precipitating problem (class I, level of evidence C), as a bridge to transplant or LVAD in candidates with refractory symptoms on oral and device therapy (class IIa, level of evidence C), and state that inotropes can be considered for palliative therapy or in hospitalized patients with low output state (class IIb, level of evidence B).

In our study, with contemporary HF management, patients who had inotrope-dependent advanced HF but were not...
2 infusion companies. However, electronic record rollout and assignments of patients to infusion companies were done without regard to medical condition and would not be expected to create systematic bias. There was also no comparison group, and thus this study does not directly address whether inotropes improve or worsen survival. Such a group would be difficult to create given current practice: many patients who present in shock or low output states acutely benefit from inotropes, have symptomatic and hemodynamic deterioration with inotrope wean, and may not survive hospital discharge without inotropes.\textsuperscript{5,6}\textsuperscript{41} This role of inotropes in stabilizing end-organ function is illustrated by the inclusion of inotropes in the heart transplant listing process.\textsuperscript{42} In this setting, it would be unusual to have a comparable noninotrope group in routine clinical practice.

In summary, inotropic agents provide symptomatic benefit in advanced HF. Survival, although still suboptimal, is somewhat better than reported in previous studies. Inotropes may be used for rescue or as a short- and intermediate-term strategy to improve hemodynamics and maintain end-organ function until LVAD or transplant. Despite their risks, inotropes continue to have a role in a selected population of patients with end-stage HF.

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### Disclosures

None.

### References


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