Left Ventricular Assist Device as Destination for Patients Undergoing Intravenous Inotropic Therapy
A Subset Analysis From REMATCH (Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure)

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Background—Left ventricular assist devices (LVADs) have improved survival in patients with end-stage heart failure. Compared with previous trials, the Randomized Evaluation of Mechanical Assistance in Treatment of Chronic Heart Failure (REMATCH) trial enrolled patients with more advanced heart failure and high prevalence of intravenous inotropic therapy. This study analyzes, on a post hoc basis, outcomes in patients undergoing inotropic infusions at randomization.

Methods and Results—Of 129 patients randomized, 91 were receiving intravenous inotropic therapy at randomization to LVAD or optimal medical management (OMM). Mean systolic pressure was 100 versus 107 mm Hg in those not receiving inotropes, serum sodium was 134 versus 137 mEq/L, and left ventricular ejection fraction was 17% for both groups. LVADs improved survival throughout follow-up for patients undergoing baseline inotropic infusions ($P = 0.0014$); for the LVAD group versus the OMM group, respectively, 6-month survival was 60% versus 39%, 1-year survival rates were 49% versus 24%, and 2-year survival rates were 28% versus 11%. For 38 patients not undergoing inotropic infusions, 6-month survival was 61% for those with LVADs and 67% for those with OMM, whereas 1-year rates were 57% and 40%, respectively ($P = 0.55$). Quality-of-life scores for survivors improved. Median days out of hospital for patients on inotropic therapy at randomization were 255 with LVAD and 105 with OMM.

Conclusions—Despite severe compromise, patients undergoing inotropic infusions at randomization derived major LVAD survival benefit with improved quality of life. Patients not undergoing inotropic infusions had higher survival rates both with and without LVAD, but differences did not reach significance. Future studies should prespecify analyses of inotropic and other therapies to determine how disease severity and parallel medical treatment influence the benefits offered by mechanical circulatory support. (Circulation. 2004;110:975-981.)

Key Words: heart failure transplantation heart-assist device

The increasing sophistication of therapies developed for heart failure requires more precise definition of subpopulations for whom the risk-benefit ratio is favorable. Advanced heart failure has been defined as persistent symptoms that limit daily life (New York Heart Association class III and IV) despite recommended therapies.1 Because cardiac transplantation in the United States was anticipated to be performed in fewer than 2400 of these patients in 2003, most patients with refractory heart failure (stage D)2 could not undergo this procedure. The successful use of left ventricular assist devices (LVADs) as a “bridge” to transplantation for extended periods of time1 led to consideration for “destination” therapy,4 as originally envisioned for the artificial heart development program.

The Randomized Evaluation of Mechanical Assistance in Treatment of Congestive Heart Failure (REMATCH) trial tested the hypothesis that the LVAD would prolong survival compared with optimal medical management (OMM) in patients ineligible for cardiac transplantation.5 Having demonstrated 48% mortality reduction in a trial of 129 patients, it

Received June 23, 2003; de novo received December 22, 2003; revision received April 15, 2004; accepted April 19, 2004.

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Circulation is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000139862.48167.23
is crucial to place these patients in context among the 50,000 to 100,000 patients with refractory heart failure currently envisioned as potential candidates for cardiac replacement. The observed mortality rates of 75% and 92% with OMM at 1 and 2 years, respectively, were higher than projected, but the 71% prevalence of intravenous inotropic infusions at randomization was also unanticipated. The use of inotropic therapy for palliation is increasing as more patients survive to develop refractory symptoms of end-stage heart failure. The purpose of this analysis of the REMATCH trial was to compare, post hoc, the profiles and outcomes in patients on and off intravenous inotropic therapy at the time of randomization.

Methods

Patient Population

The REMATCH study was conducted at 20 experienced centers that enrolled 129 patients between May 1998 and July 2001, with the International Center for Health Outcomes and Innovation Research at Columbia University (InCHOIR) as an independent coordinating center. The study was sponsored under a cooperative agreement between Columbia University, the National Heart, Lung, and Blood Institute, and Thoratec Corporation.

Entry criteria included left ventricular ejection fraction ≤25% with severe heart failure symptoms (New York Heart Association class IV) for ≥90 days despite attempted therapy with ACE inhibitors, diuretics, and digoxin. Severe limitation had to be documented by peak oxygen consumption of ≤12 mL · kg⁻¹ · min⁻¹ with evidence of anaerobic metabolism, or by dependence on intravenous inotropic agents supported by completion of a weaning failure form. Enrollment criteria were broadened at 18 months to allow class IV symptoms for 60 of the last 90 days and peak oxygen consumption of ≤14 mL · kg⁻¹ · min⁻¹, but only 3 patients qualified only by the relaxed criteria. To minimize later transplantation, ineligibility was for presumably irreversible contraindications such as advanced age, diabetes with end-organ damage, or creatinine >2.5 mg/dL for ≥90 days, as detailed previously.

“Dependence” on intravenous inotropic therapy required documentation of a weaning trial, which was done for 64 patients. The weaning form included time and doses of inotropes, with indicated cause of weaning failure as hypertension (systolic pressure below 80 mm Hg), deterioration in renal function, and/or heart failure, defined by worsening symptoms with objective findings. When weaning failure was not documented, eligibility required peak oxygen consumption <12 to 14 mL · kg⁻¹ · min⁻¹ within 90 days. When qualifying by exercise testing, patients may subsequently have become dependent on inotropic therapy without requiring documented weaning failure, and thus true dependence may have been higher than reported. For survival analyses, patients who did not complete documented weaning attempts but were receiving ≥2 inotropic infusions were considered dependent on such therapy.

Therapy After Randomization

Patients were assigned in 1:1 randomization to receive either LVAD or OMM. Patients randomized to LVAD underwent implantation and subsequent care as described previously. Cardiologists credentialed for inpatient and outpatient experience and participation in heart failure trials supervised OMM. The emphasis of OMM was survival without suffering, with specific approaches to this population drafted by the REMATCH cardiologists, with additional review from Dr G. Francis (Cleveland Clinic Foundation, Cleveland, Ohio). These will be reported elsewhere but included detailed strategies for weaning from inotropic infusions with strong recommendations to avoid chronic inotropic therapy.

Quality-of-Life Assessment

Functional status and quality of life were assessed with the Minnesota Living With Heart Failure Questionnaire, the prespecified subscales of physical function and emotional role of the Short-Form General Health Survey (SF-36), and the New York Heart Association classification.

Statistical Analysis

All-cause mortality was the primary end point, with primary analysis planned when the trial reached 92 deaths. Group survival was compared with the log-rank statistic. The Cox proportional-hazards model was used to estimate relative risks. The subgroup analysis for patients taking intravenous inotropes was prompted by the high prevalence of inotrope use at randomization. Quality of life was assessed at 1 year, with ANCOVA for differences in the quality of life in survivors, after adjustment for baseline values. The data set used for this publication was closed on June 20, 2002.

Results

Patient Populations

The trial enrolled 129 patients, of whom 68 were randomized to LVAD and 61 to OMM. Intravenous inotropic therapy was reported at randomization in 91 patients (71%). Two or more agents were administered at randomization in 43% of patients. Dobutamine was the most common agent, in 75% of patients, with milrinone in 43% and dopamine in 30% of patients. Failure of weaning was documented for 64 patients. For 19 of these, criteria for weaning failure were documented despite ongoing inotropic support, and no dose decrease was attempted. In 8 patients, the weaning attempt was of one agent during continued infusion of another, and in 3 other patients, one agent was substituted unsuccessfully for another. In the remaining 34 patients, the inotropic dose was decreased during the documented weaning attempt. Inability to wean was attributed to hypotension in 59% of the dependent patients (mean systolic blood pressure 73 mm Hg), renal dysfunction in 21%, and/or deteriorating heart failure in 78%. The most common symptom was worsening dyspnea at rest. In 8 patients without description of worsening symptoms, mean cardiac indices of 1.0 to 1.5 L · min⁻¹ · m⁻² were documented.

The 27 patients undergoing inotropic infusions at randomization without documented weaning attempts all qualified for inclusion on the basis of peak oxygen consumption, which was 9.2±2.1 mL · kg⁻¹ · min⁻¹. Only 1 patient in the group qualified with peak oxygen consumption of between 12 and 14 mL · kg⁻¹ · min⁻¹. Because the decision to attempt weaning and the determination of weaning failure were not standardized, the major analysis was performed for all patients undergoing intravenous inotropic infusions at randomization. Among these patients, randomization was to LVAD in 45 and to OMM in 46.

Mean age was 68 years, and mean left ventricular ejection fraction was 17% for patients with and without baseline inotropic therapy (Table 1). Patients receiving inotropic therapy had lower systolic pressure (100 versus 107 mm Hg) and lower serum sodium (134 versus 137 mEq/L). Differences between the 2 populations are underestimated by baseline measurements, which reflect ongoing inotropic support for the inotropic group. The patients undergoing inotropic infusions who met enrollment criteria because of low
peak oxygen consumption rather than dependence by failed weaning attempts had an intermediate profile of severity (Table 1).

All patients were evaluated carefully with regard to further therapeutic options. For patients undergoing inotropic infusions at randomization, infusions were discontinued by discharge in 18 (20%) and consolidated from more than 1 infusion to a single infusion in an additional 9 patients (10%). Patients were seen at least monthly after discharge, with the same number of visits in both randomized groups.

Survival Analysis

OMM Patients Only

The Kaplan-Meier survival analysis (Figure 1) was performed for medical management patients, stratified by initial inotrope use (Figure 2A). Survival at 1 year was 40% for 15 patients not undergoing inotropic therapy at randomization compared with 24% in the 46 patients undergoing inotropic therapy (difference 16.19%, with 95% confidence limits −11.5%, 43.9%; P = 0.108). Patients receiving inotropes who were considered dependent on intravenous inotropic infusions on the basis of completed weaning forms or the use of 2 or more simultaneous inotropic infusions had a 19% 1-year survival rate.

LVAD Patients Only

Survival after LVAD therapy was not significantly affected by use of intravenous therapy at the time of randomization, before LVAD implantation (P = 0.55). At 1 year, the no-inotrope group (23 patients) had 57% survival with LVADs (Figure 2B), and the inotrope group (45 patients) had 49% survival (difference 7.6%, 95% confidence limits −17.4%,

| TABLE 1. Baseline Characteristics in Relation to Inotropic Therapy |
|---------------|---------------|---------------|---------------|---------------|
|               | No Intravenous Inotropic Therapy | Intravenous Inotropic Therapy | Inotrope Dependent | Receiving Inotropes Without Documented Dependence |
| No.           | 38            | 91            | 64            | 27            |
| Age, y        | 68±7          | 67±9          | 67±9          | 66±9          |
| LVEF, %       | 17±4          | 17±5          | 18±5          | 17±5          |
| SBP, mm Hg    | 107±16        | 100±16        | 98±17         | 102±12        |
| Na, mEq/L     | 137±4         | 134±6*        | 133±6         | 135±5         |
| PCW, mm Hg    | 22±10         | 25±9*         | 26±9          | 23±7          |
| Cardiac index, L·min⁻¹·m⁻² | 1.9±0.5       | 2.0±0.6       | 2.0±0.6       | 2.1±0.6       |
| Creatinine, mg/dL | 1.8±0.6       | 1.8±0.6       | 1.8±0.7       | 1.8±0.7       |
| RAP, mm Hg    | 12±6          | 12±8          | 13±8          | 11±7          |
| Diuretic use, % | 100           | 95            | 92            | 100           |
| >1 Diuretic, % | 50            | 52            | 52            | 52            |
| β-Blockers, % | 34            | 16            | 13            | 26            |
| ACE inhibitors, % | 66            | 53            | 50            | 59            |

LVEF indicates left ventricular ejection fraction; SBP, systolic blood pressure; PCW, pulmonary capillary wedge pressure; and RAP, right atrial pressure.

*Significant difference between patients undergoing intravenous inotropic therapy and patients not undergoing intravenous inotropic therapy at time of randomization.

Figure 1. Four Kaplan-Meier survival curves stratified by randomization to LVAD and OMM and by intravenous inotropic infusions at the time of randomization. For the 91 patients on intravenous inotropic (INO) therapy at randomization, major survival benefit was seen with LVAD compared with OMM (bottom line), with 48% versus 24% survival at 1 year and 28% versus 11% at 2 years (P = 0.0014, log rank). For the 38 patients not on baseline inotropic infusions (NO INO), survival at 2 years was 22% with LVAD and 16% with OMM (P = 0.55).
Figure 2. Pairs of curves highlighted and expanded from Figure 1. A, Actuarial survival for OMM patients stratified by baseline inotropic use. Patients receiving intravenous inotropic therapy at baseline (n=46) are compared with those not receiving intravenous inotropic therapy at baseline (n=15; P=0.108, log rank). Late survival on medical management as shown includes survival for 3 patients who received LVADs after study termination. B, Actuarial survival for LVAD patients stratified by baseline inotropic use. Patients receiving intravenous inotropic therapy at randomization (n=45) are compared with those not receiving intravenous inotropic therapy at randomization (n=23; P=0.555, log rank). C, Actuarial survival for patients receiving intravenous inotropic therapy at time of randomization stratified by randomization to LVAD or OMM. INO indicate intravenous inotropic therapy; NO INO, no inotropic infusions at baseline.
32.6%). Within the latter group, the 34 patients with defined dependence had 41% 1-year survival.

All Patients Undergoing Intravenous Inotropic Therapy

When outcomes for the 91 patients undergoing inotropic therapy at randomization were examined, there was a major survival benefit seen with the LVAD compared with OMM ($P = 0.0014$). Survival early after randomization (postoperative period for LVAD patients) was similar in both groups, after which the curves diverged and remained separate (Figure 2C). At 1 year, survival with LVAD was 49% versus 24% for OMM, and by 2 years, 28% were alive in the LVAD group compared with 11% in the OMM group.

Patients Not Undergoing Intravenous Inotropic Therapy

For the small group of patients ($n = 38$) not undergoing intravenous inotropic therapy at randomization, survival was 61% with LVADs and 67% with OMM at 6 months (Figure 1). By 12 months, survival was 57% with LVADs and 40% with OMM, and at 2 years, the rates were 22% and 16%, respectively ($P = 0.55$).

Quality of Life for Survivors

Survivors had improved quality of life after LVAD implantation. Patients undergoing inotropic therapy at randomization had a Minnesota Living With Heart Failure Quality of Life Score of 77, worse than in any other trial. By 1 year, the score had improved to 41 (Figure 3), but not all patients provided scores. The prespecified subscales of physical function and emotional role of the SF-36 also showed substantial improvements. Improvements in these measures were comparable for all LVAD survivors, regardless of inotropic therapy use. There was also a trend for improvement in quality of life for patients who survived 1 year without an LVAD, both in the 5 one-year survivors not undergoing initial inotropic infusions and in the 8 patients undergoing initial infusions, but the numbers were too small to compare. For patients undergoing intravenous inotropic therapy at randomization, median days alive out of hospital were 255 with LVAD and 105 for OMM.

Discussion

The patients in REMATCH presented greater severity of clinical and hemodynamic compromise and higher mortality rates than patients in any previous heart failure trial (Table 2). The population was dominated by patients undergoing intravenous inotropic infusions at randomization, who, despite the severity of their illness, derived major survival and quality-of-life advantages from LVAD implantation.

REMATCH Population: High Predicted Mortality

Patients enrolled had an average age of 68 years, older than patients in most heart failure trials. Most patients were decompensated and unstable at enrollment, conditions that have been exclusion criteria for trials that demonstrated the benefit of ACE inhibitors and β-blocking agents. Even compared with trials in hospitalized patients, the REMATCH population enrolled patients with more compromise, indicated by lower blood pressure and serum sodium and higher creatinine levels.

Patients receiving inotropic infusions at entry had more adverse prognostic indicators than those taking oral therapy alone, despite ongoing inotropic support. A high mortality rate would have been expected for this group solely on the basis of the low sodium and systemic pressure observed in these patients. In the Flolan International Randomized Survival (FIRST) trial, the left ventricular ejection fraction of 19%, systolic pressure of 105 mm Hg, and serum sodium of 137 mEq/L showed that these patients were less compromised than those in REMATCH, but mortality was still high (37% at 6 months). The subgroup of patients in FIRST who received continuous dobutamine infusion closely resembles

| TABLE 2. Early Mortality in Advanced Heart Failure Trial of Oral Therapies and LVAD |
|----------------------------------|----------------|----------------|----------------|----------------|----------------|
| No.                             | 127            | 527            | 841            | 1133           | 15             | 46             |
| Age, y                          | 63             | 64             | 65             | 64             | 68             | 68             |
| LVEF, %                         | ...            | 21             | 25             | 20             | 17             | 17             |
| SBP, mm Hg                      | 125            | 115            | 122            | 125            | 107            | 100            |
| Na, mEq/L                       | 137            | 139            | 137            | 137            | 134            |
| Creatinine, mg/dL               | 1.5            | 1.5            | 1.2            | 1.5            | 1.8            | 1.8            |
| 6-Month mortality, %            | 29             | 20             | 13             | 9              | 33             | 61             |
| LVEF indicates left ventricular ejection fraction; SBP, systolic blood pressure. *Populations are those undergoing ACE inhibitor therapy (CONSENSUS) with placebo for other therapies studied. |
the REMATCH population, with systolic pressure of 101 mm Hg and 6-month mortality of 71%. Mortality for REMATCH patients undergoing inotropic infusions was commensurate with other reports, with an expected 50% mortality rate at 3 to 6 months, as recently reviewed elsewhere.\textsuperscript{14}

Previous trials have shown that chronic oral inotropic therapy can itself hasten mortality.\textsuperscript{15,16} In those trials, however, it was feasible to maintain patients at home on oral therapy plus a placebo alone. Patients in the REMATCH trial instead fit the most advanced form of the recently defined “D” heart failure stage, in which severe symptoms persist despite the application of known effective therapies.\textsuperscript{2} The average cardiac index of only 2 L \( \cdot \) min\(^{-1} \cdot m^{-2} \) and the pulmonary wedge pressure of 25 mm Hg during inotropic therapy suggest that such support therapy was being used appropriately to treat severe hemodynamic compromise. There is increasing recognition of a cohort of patients who cannot be maintained on current oral therapy alone despite prolonged and repeated efforts at dedicated centers.\textsuperscript{17} Inotropic inotropic therapy has been recognized as acceptable palliation to decrease symptoms and allow hospital discharge for these patients when there are no other options.\textsuperscript{2,18}

**Major Benefit for Populations With High Heart Failure Mortality**

When compared with the high mortality rate of patients with the most severe decompensation, LVAD use conferred a clear survival benefit. Although it was anticipated that device surgery might be associated with a small excess perioperative mortality, survival in the LVAD group was equal to or better than survival in the group with medical management at all time points after randomization for patients undergoing baseline inotropic therapy. By 6 months, survival in this population was 60% with LVAD versus 39% without. At 1 year, survival was doubled by LVAD: 49% versus 24%. By 2 years, survival with LVADs was 28% compared with 11% for OMM (including 3 patients who received LVADs after study termination).

Quality-of-life measurements demonstrated similar improvements whether or not patients were randomized on the basis of inotropic therapy. Patients with LVAD who completed questionnaires indicated return to a quality of life similar to that of ambulatory patients with moderate heart failure, commensurate with New York Heart Association class II to III. Although the baseline Minnesota Living With Heart Failure score of 77 for REMATCH was worse than in previous trials, the quality-of-life score achieved was 41 for LVAD patients compared with 59 at baseline and 44 at 6 months after biventricular pacing,\textsuperscript{19} a therapy recognized to improve functional capacity and quality of life.

**Current Target Populations for LVAD**

At this time in the evolution of mechanical cardiac support, the target heart failure population for LVAD is one for whom the LVAD confers a better chance of survival than current medical therapy. The criteria of persistent class IV symptoms, left ventricular ejection fraction \( \leq 25\% \), and peak oxygen consumption \( \leq 12 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) or inotrope dependence describe a large, heterogeneous population. This analysis suggests that patients receiving intravenous inotropic therapy from experienced heart failure/transplant cardiologists can expect a doubling in survival rate to 50% at 1 year with LVAD as provided in REMATCH. Patients with lower expected mortality who are undergoing medical therapy, such as those eligible for recent \( \beta \)-blocker trials, would be expected to derive less survival benefit from a therapy with <50% 2-year survival.

If other populations could be identified with similarly high predicted mortality rates, they might have derived a benefit similar to that seen in this trial. Other predictors of high early mortality may be identified that will define a target population even without inotropic therapy. Systolic blood pressure, serum sodium, renal function, and very high natriuretic peptide levels might be combined to predict mortality for this population. Discontinuation of ACE inhibitors because of circulatory-renal limitations also identifies a high-risk population.\textsuperscript{20} Conversely, not all patients with inotropic infusions would necessarily have similarly poor outcomes with subsequent medical management, because many who receive inotropic infusions during hospitalization can undergo successful transition to oral therapies, with 6-month survival rates better than those currently reported with LVAD use.\textsuperscript{21}

The ideal characteristic for selection of LVAD candidates would identify high early mortality without LVAD use but would not itself diminish the likelihood of a good outcome with LVAD. Does dependence on inotropic therapy define patients who are “too sick” for LVAD placement as permanent destination therapy? In patients with progressive decompensation, protracted inotropic support or repeated failed weaning may close the window of opportunity for successful destination therapy. In the present trial, 19 patients were considered too compromised for any weaning attempt. Patients considered dependent by documented weaning failure or use of 2 inotropic agents simultaneously had a 1-year survival rate of 41% with the LVAD, which was less than the 57% rate for patients taking oral medical therapy only but still much higher than the 19% on medical management for those dependent patients. These comparisons are illustrative only, because the small subset size precludes confidence in the survival estimates.

**Limited Generalization of REMATCH Results**

REMATCH was not designed to address whether inotropic dependence should affect candidacy for LVAD implantation. Randomization was not stratified on the basis of inotrope use, and enrollment data did not capture inotropic dependency status in all patients. Although weaning was strongly advocated in the medical management strategies, there was not a consensus on whether neurohormonal antagonists should be discontinued when hypotension led to chronic inotropic support. It is not possible to determine whether there were alternative medical strategies to replace inotropic infusions for some of these patients. Adherence to guidelines, when applicable, and extensive experience of the cardiologist investigators defined medical management for these patients.

Comparison with other patients is also complicated by the inclusion criterion that patients have irreversible contraindi-
tions for transplantation, to decrease crossover to transplantation. This requirement for REMATCH is not relevant to clinical application. Actual practice will likely often reflect a hybrid of bridging and destination.

The present study serves as a template for consideration of issues that will be involved as mechanical cardiac support technology evolves. Analyses of the small groups categorized by inotrope use or other indices of decompensation generate rather than prove hypotheses about selection of patients for approved LVADs. Characteristics that identify patients at high risk on medical therapy but that do not compromise post–device implantation survival will help to define populations with anticipated benefit as observed in REMATCH. The specific details, however, rapidly become less relevant. The device used in the REMATCH trial has already been replaced by a later-generation device, modified to decrease the risks of complications. At the same time, lessons from this trial have inspired new protocols to improve nutrition and prevent device-related infection. As these advances translate into measurable improvement in device outcomes, a wider margin of benefit will encourage broader indications for LVAD implantation to improve survival and quality of life.

Acknowledgment

The study was sponsored cooperatively by the National Institutes of Health and Thoratec Corporation.

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*Circulation.* 2004;110:975-981; originally published online August 16, 2004; doi: 10.1161/01.CIR.0000139862.48167.23

*Circulation* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

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