

Combined Oral Positive Inotropic and Beta-Blocker Therapy for Treatment of Refractory Class IV Heart Failure

SIMON F. SHAKAR, MD, WILLIAM T. ABRAHAM, MD, FACC, EDWARD M. GILBERT, MD, FACC,* ALASTAIR D. ROBERTSON, PhD, BRIAN D. LOWES, MD, LAWRENCE S. ZISMAN, MD, DEBRA A. FERGUSON, BSN, MICHAEL R. BRISTOW, MD, PhD, FACC

Denver, Colorado and Salt Lake City, Utah

Objectives. We sought to assess the effects of combined oral positive inotropic and beta-blocker therapy in patients with severe heart failure.

Background. Patients with severe, class IV heart failure who receive standard medical therapy exhibit a 1-year mortality rate >50%. Moreover, such patients generally do not tolerate beta-blockade, a promising new therapy for chronic heart failure. Positive inotropes, including phosphodiesterase inhibitors, are associated with increased mortality when administered over the long term in these patients. The addition of a beta-blocker to positive inotropic therapy might attenuate this adverse effect, although long-term oral inotropic therapy might serve as a bridge to beta-blockade.

Methods. Thirty patients with severe heart failure (left ventricular ejection fraction [LVEF] $17.2 \pm 1.2\%$, cardiac index 1.6 ± 0.1 liter/min per m^2) were treated with the combination of oral enoximone (a phosphodiesterase inhibitor) and oral metoprolol at two institutions. Enoximone was given at a dose of ≤ 1 mg/kg body weight three times a day. After clinical stabilization, metoprolol was initiated at 6.25 mg twice a day and slowly titrated up to a target dose of 100 to 200 mg/day.

Results. Ninety-six percent of the patients tolerated enoximone, whereas 80% tolerated the addition of metoprolol. The mean duration of combination therapy was 9.4 ± 1.8 months. The mean length of follow-up was 20.9 ± 3.9 months. Of the 23 patients receiving the combination therapy, 48% were weaned off enoximone over the long term. The LVEF increased significantly, from $17.7 \pm 1.6\%$ to $27.6 \pm 3.4\%$ ($p = 0.01$), whereas the New York Heart Association functional class improved from 4 ± 0 to 2.8 ± 0.1 ($p = 0.0001$). The number of hospital admissions tended to decrease during therapy ($p = 0.06$). The estimated probability of survival at 1 year was $81 \pm 9\%$. Heart transplantation was performed successfully in nine patients (30%).

Conclusions. Combination therapy with a positive inotrope and a beta-blocker appears to be useful in the treatment of severe, class IV heart failure. It may be used as a palliative measure when transplantation is not an option or as a bridge to heart transplantation. Further study of this form of combined therapy is warranted.

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Chronic heart failure due to left ventricular (LV) systolic dysfunction is a progressive disease syndrome that continues to be associated with high rates of morbidity and mortality, despite recent advances in medical therapy (1-4). In patients with New York Heart Association (NYHA) functional class IV heart failure, the 1-year mortality rate exceeds 50% despite aggressive therapy with angiotensin-converting enzyme (ACE) inhibitors (2). Long-term beta-adrenergic receptor blockade is a promising new approach to the treatment of heart failure (3-8). However, beta-blockers are difficult and often impossible to use in patients with advanced heart failure (3,9,10), and

consequently very limited data are available in this setting. Several positive inotropic agents have been used to treat chronic heart failure; unfortunately, most of them have been shown to increase mortality (11-13). This effect of long-term positive inotropic therapy to increase heart failure mortality is especially apparent in patients with advanced heart failure (11).

Because neurohormonal activation appears to play a pivotal role in the progression of disease and mortality in patients with heart failure (14-16), we postulated that adding a beta-blocker to a positive inotrope would 1) permit successful initiation and up-titration of beta-blockade; and 2) prevent the deleterious effects on survival associated with long-term positive inotropic therapy.

We describe our experience with the addition of metoprolol to enoximone (17), an oral phosphodiesterase inhibitor, in a series of 30 patients with chronic, severe and medically refractory heart failure. Tolerability and the effects on LV function, symptoms, hospital admission and survival are reviewed.

From the Department of Medicine, Division of Cardiology, University of Colorado Health Sciences Center, Denver, Colorado; and *Department of Medicine, Division of Cardiology, University of Utah, Salt Lake City, Utah.

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Address for correspondence: Dr. Michael R. Bristow, Campus Box B-139, University of Colorado Health Sciences Center, 4200 East 9th Avenue, Denver, Colorado 80262. E-mail: michael.bristow@uchsc.edu.

Abbreviations and Acronyms

ACE	= angiotensin-converting enzyme
CONSENSUS	= Cooperative North Scandinavian Enalapril Survival Study
EF	= ejection fraction
LV	= left ventricle, left ventricular
NYHA	= New York Heart Association
PROMISE	= Prospective Randomized Milrinone Survival Evaluation

Methods

Patient group. Thirty patients with functional class IV heart failure due to LV systolic dysfunction were evaluated. Patients selected for enoximone therapy were either receiving intravenous inotropes and had failed at least two attempts at inotrope withdrawal (n = 18 [60%]) or were too sick and unstable to tolerate beta-blockade in the opinion of the staff specialist in heart failure (n = 9 [30%]). This subset of patients spent an average of 32 days in the hospital per year, and ultimately three of them had heart transplants and six could not be weaned off enoximone or had previously not responded to a beta-blocker (n = 3 [10%]). Their available records between October 1984 and November 1996 were reviewed for this report. Eighteen of these patients were treated at the University of Utah and 12 at the University of Colorado. All patients gave written, informed consent to participate in a compassionate-use study of enoximone. The consent form was reviewed and approved by the local Institutional Review Board. Table 1 presents the selected characteristics of these patients with heart failure. A left ventricular ejection fraction (LVEF) was available for all patients at baseline (by echocardiography in 2 patients, by LV angiography in 2 patients and by gated blood pool scan in 26 patients) and for 20 patients at the time of final analysis (all by gated blood pool scan).

Treatment protocol. There were five phases of treatment: 1) *Stabilization of the patient with enoximone:* Inpatients were either slowly weaned from intravenous dobutamine or other

intravenous inotropes, and outpatients were admitted to the hospital for 36 to 48 h to start oral enoximone. The starting dose of enoximone was usually 1 to 2 mg/kg body weight per day in three divided doses. Once ambulation was possible, the patient was discharged. 2) *Optimization of heart failure therapy as an outpatient:* Patients received digitalis, diuretic agents and vasodilators (mostly ACE inhibitors). 3) *Institution of beta-blockade:* Metoprolol was started at 6.25 mg orally twice a day and then gradually increased to a target dose of 100 to 200 mg/day in two or three divided doses. In a few patients, a once-daily formulation (Toprol XL, Astra) was used. 4) *Attempted withdrawal of enoximone:* After the patient was stable on the combination therapy for 2 to 4 months, withdrawal of enoximone was attempted over a period of 2 to 3 weeks. If the patient's condition deteriorated, the dose was restored to its previous level. 5) *Long-term therapy:* Patients received either metoprolol alone or the combination when enoximone could not be weaned. This phase lasted indefinitely or until heart transplantation or death.

Statistical analysis. SAS software (SAS Institute) was used for all statistical analyses. All tests were two-sided, and the significance level was at 0.05. When appropriate, data are expressed as the mean value ± SEM. Paired data (at baseline and during treatment) were analyzed using the paired *t* test or, if the distribution of the paired differences was not normal, by the sign test.

Survival curves and confidence intervals were estimated using the actuarial method. Survival data for patients undergoing heart transplantation were censored at the time of transplantation. The survival curves from the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) and the Prospective Randomized Milrinone Survival Evaluation (PROMISE) were estimated from published data. Using the log-rank test, they were compared with the survival data for our patients.

Results

Treatment tolerability. Twenty-nine (96%) of the 30 patients tolerated long-term oral enoximone therapy. One patient was withdrawn from enoximone 5 months after initiation because of a syncopal episode that occurred at home without documented arrhythmia. All 18 patients who were receiving intravenous inotropes at baseline were successfully transitioned to oral enoximone. Twenty-four patients (80%) tolerated beta-blockade with metoprolol; five patients did not; and one patient had a heart transplant before metoprolol could be started. Of the 23 patients on combination therapy, 11 (48%) were weaned off enoximone, whereas 12 (52%) were considered stable on the combination, as assessed by clinical deterioration when enoximone was stopped. The mean dose of enoximone was 189 ± 13 mg/day (range 75 to 300). The mean dose of metoprolol in the 24 patients who tolerated the drug was 113 ± 9 mg/day (range 37.5 to 200). The patients' mean length of time on combination therapy was 9.4 ± 1.8 months (range 0.1 to 38.6). The patients' mean length of follow-up

Table 1. Baseline Characteristics of 30 Study Patients

Age (yr)	53 ± 2.9
Men/women	22/8
Etiology of CMP	
IDC	23 (77%)
Ischemic	4 (13%)
Valvular	2 (7%)
Anthracycline	1 (3%)
NYHA functional class IV	30 (100%)
LVEF (%)	17.2 ± 1.2
HR (beats/min) (n = 28)	101 ± 4
PCWP (mm Hg) (n = 14)	25.2 ± 1.5
CI (liter/min per m ²) (n = 14)	1.6 ± 0.1

Data presented are mean value ± SEM or number (%) of patients. CI = cardiac index; CMP = cardiomyopathy; HR = heart rate; IDC = idiopathic dilated cardiomyopathy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association; PCWP = pulmonary capillary wedge pressure.

Table 2. Clinical Variables Before and During Combined Therapy

	No. of Evaluable Patients	Baseline (mean \pm SEM)	During Therapy (mean \pm SEM)	p Value
LVEF (%)	20	17.7 \pm 1.6	27.6 \pm 3.4	0.01
HR (beats/min)	26	101 \pm 4	80 \pm 4	0.0001
NYHA functional class	30	4 \pm 0	2.8 \pm 0.1	0.0001
Hospital admissions/yr	12	2.3 \pm 0.3	1.0 \pm 0.6	0.06

Abbreviations as in Table 1.

(until December 1, 1996, death or heart transplantation) was 20.9 ± 3.9 months (range 0.6 to 82.5).

Effect of treatment on clinical variables. The combination of metoprolol and enoximone improved LV function and reduced heart rate (Table 2). The LVEF was obtained after a mean of 16 ± 3 months and improved significantly in the evaluable patients. As assessed by the NYHA functional classification, combination therapy improved symptoms with a decrease in functional class ranking from 4 ± 0 to 2.8 ± 0.1 ($p < 0.0001$) (Table 2). On therapy, 5 patients were in functional class IV, 16 were in class III, 8 were in class II and 1 was in class I. There was also a trend ($p = 0.06$) toward reduction in the number of hospital admissions in the year after compared with the year before initiation of treatment in the 12 patients for whom this data were fully available. Before initiation of therapy, one patient was admitted to the hospital for 4 continuous months and received intravenous inotropes, but remained out of the hospital after combined therapy.

Clinical outcome. The clinical outcomes of all 30 patients are summarized in Table 3. This includes the six patients who did not have long-term beta-blockade, five of whom had heart transplants. Six patients died: one from small-cell carcinoma of the lung, three from worsening heart failure and two with sudden death. Figure 1 shows the intention-to-treat actuarial survival curve of the 30 patients. Estimated survival rates (95% confidence interval) are 96% (88% to 100%) at 6 months, 81% (64% to 98%) at 1 year and 69% (49% to 90%) at 2 years. These results are significantly better ($p = 0.01$) than those for the enalapril-treated patients in functional class IV (approximate 1-year actuarial survival rate 54%) in CONSENSUS (2), in which enalapril was found to be significantly better than placebo. Similarly, these results are significantly better ($p = 0.03$) than those for the patients in functional class IV who received standard therapy (approximate 1-year actuarial survival rate 61%) in PROMISE (11), in which standard therapy was found to be significantly better than milrinone. Figure 2 shows the estimated survival curves for the three studies.

Table 3. Clinical Outcomes of Patients at Time of Last Follow-Up (mean 20.9 ± 3.9 months)

	No. (%) of Patients
Alive without heart transplantation	15 (50.0)
Alive with heart transplantation	9 (30.0)
Cardiac death	5 (16.7)
Noncardiac death	1 (3.3)

Discussion

Rationale for use of the combination positive inotrope/beta-blocker therapy. The increase in mortality associated with long-term inotropic therapy has been attributed to a proarrhythmic effect (11-13,18,19) contributing to an increased rate of sudden death (20) and to direct myocyte toxicity with acceleration of disease progression (11,18-22). At the molecular level, this toxicity may be related to cyclic adenosine monophosphate-mediated calcium overload (23).

Beta-blockers have been shown to attenuate these changes at the molecular (23) and the cellular (21) level. Substantial data now support their usefulness in the pharmacologic management of chronic heart failure (3,6,7,24). Beta-blockers may also reduce the risk of sudden cardiac death (25) and slow the heart rate. For these and other reasons, they may be ideal in attenuating the undesirable side effects of positive inotropes (26,27). In contrast, phosphodiesterase inhibitors, unlike beta-receptor agonists, would be expected to retain their positive inotropic and vasodilator effects in the presence of beta₁-selective blockade, because their site of action is beyond the beta-adrenergic receptor, and the vasodilator as well as some positive inotropic effects of endogenous catecholamines are beta₂-receptor mediated. Thus, the addition of a beta-blocker to a phosphodiesterase inhibitor would be expected to eliminate or attenuate the negative inotropic side effects of the former and the long-term adverse effects of the latter.

In patients with severe heart failure who do not tolerate beta-blockers, we chose enoximone as the positive inotropic agent to be used in combination, because at a low dose it produces enough improvement in cardiac function to allow for

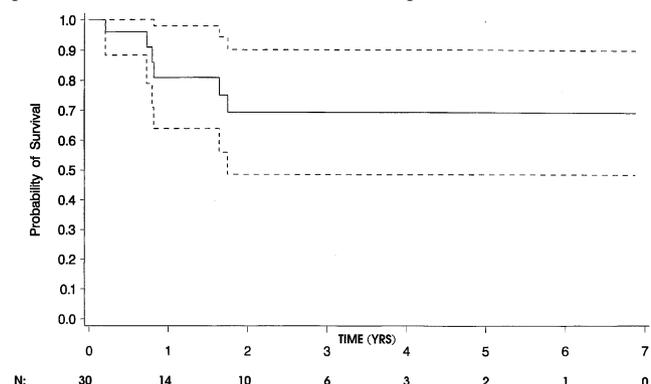
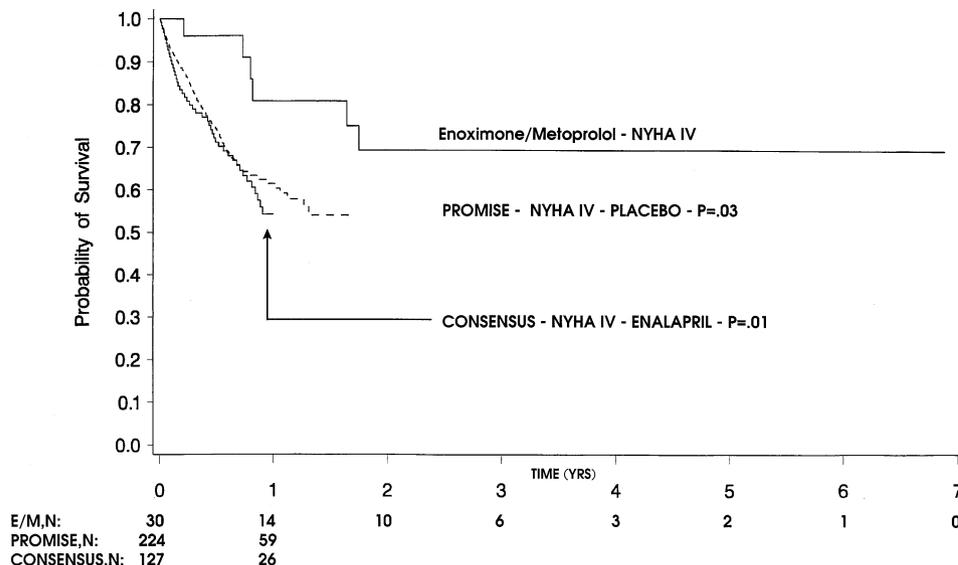
Figure 1. Survival probability, with 95% confidence limits, for all patients treated with enoximone and metoprolol.

Figure 2. Comparison of the survival probability curves of our patients treated with enoximone (E) and metoprolol (M) with those of placebo-treated patients in NYHA functional class IV in the PROMISE trial and enalapril-treated patients in the CONSENSUS trial.



the use of the beta-blocker (28,29). The use of a drug such as enoximone is favored because it is available orally, because it has been used successfully to wean patients from inotropes (30) or to bridge them to heart transplantation (31) and because its mechanism of action has been shown to bypass the beta-receptor and to produce an inotropic effect even with beta-blockade (32-34).

In our series of 30 patients, we found that treatment with a combination of enoximone and metoprolol improved LV function and NYHA functional class and tended to reduce hospital admissions. The mortality associated with this regimen was better than that observed in CONSENSUS for patients treated with enalapril or in PROMISE for placebo-treated patients in functional class IV.

Study limitations. The most important limitation of our study is its retrospective nature, with all the bias that this introduces and the incomplete set of data. The absence of a control group does not allow for direct comparisons of survival curves. Another potential weakness is the use of heart transplantation in 30% of the patients, which may have improved the estimated survival rates, although these patients were censored at the time of transplantation. Alternatively, all of these patients may have required heart transplantation had they not improved while taking enoximone and metoprolol.

Clinical implications. In patients with end-stage heart failure, heart transplantation is usually offered as the ultimate therapeutic option to improve survival. However, many patients are not candidates for transplantation, and donor organs are scarce. Our data suggest that combined enoximone/metoprolol therapy is tolerable and might be a potential and useful therapy in patients with severe heart failure. However, larger, prospective trials comparing this therapy with placebo plus conventional treatment will be required to demonstrate the effectiveness of this approach. If validated, this therapy should be cost-effective and might reduce the number of

patients waiting for heart transplantation or delay this eventuality.

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