The Impact of Beta-Receptor Blocker Addition to High-Dose Angiotensin-Converting Enzyme Inhibitor-Nitrate Therapy in Heart Failure

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Summary

Background: The natural history of heart failure is one of continued worsening of cardiac function. Beta-receptor blocker therapy has been effective in improving clinical status and left ventricular function in patients with heart failure. Similarly, high doses of angiotensin-converting enzyme (ACE) inhibitors with nitrates partially reverse the ventricular remodeling of heart failure.

Hypothesis: We tested the hypothesis that beta-blocker therapy added to high-dose ACE inhibitor-nitrates would potentiate the reversal of heart failure.

Methods: Thirteen patients, aged 52 ± 8 years, with moderate to severe heart failure, 12 of whom were referred for transplant consideration, with heart failure duration of 4.8 ± 2.2 years, were prospectively followed for 12 months. Baseline echocardiographic ejection fraction was $19 \pm 8\%$, and presenting New York Heart Association class was 2.9 ± 0.7 . Angiotensin-converting enzyme inhibitors and nitrates were uptitrated over 6 months to a final dose of lisinopril 53 ± 31 mg/day, and isosorbide dinitrate 217 ± 213 mg/day. At 6 months, beta-blocker therapy with atenolol was initiated and titrated to a final dose of 46 ± 23 mg/day. Two-dimensional Doppler echocardiography and metabolic stress testing were performed at baseline, at 6 months on lisinopril-nitrates only, and at 12 months on combined ACE inhibitor-nitrate and beta-blocker therapy.

Results: New York Heart Association classification improved from 2.9 ± 0.7 to 1.8 ± 0.8 on lisinopril-nitrates ($p < 0.05$), and to 1.5 ± 0.5 with the addition of beta blockade ($p = \text{NS}$). On follow-up, peak oxygen consumption rose from 17 ± 7 ml $\text{O}_2/\text{kg}/\text{min}$ at baseline to 21 ± 5 ml $\text{O}_2/\text{kg}/\text{min}$ at 6 months on lisinopril-nitrates ($p = 0.06$) without further change on beta blockade. Ejection fraction rose from 19 ± 8 to $33 \pm 14\%$ on lisinopril-nitrates at 6 months ($p = 0.005$) and to $36 \pm 18\%$ on beta blockade at 12 months ($p = \text{NS}$).

Conclusion: High-dose ACE inhibitor-nitrate therapy significantly improved patient clinical status and left ventricular systolic function in heart failure. The addition of beta-receptor blockade over and above high-dose ACE inhibitor-nitrates was well tolerated but had no further impact on symptomatic status, exercise tolerance, or left ventricular systolic function. The potential for pharmacologic reversal of heart failure remodeling may be finite despite the use of complementary therapies. Larger placebo-controlled and randomized trials of beta-receptor blockade added to high-dose ACE inhibitor-nitrate therapy are needed to confirm these observations.

Key words: angiotensin-converting enzyme inhibitors, nitrates, beta-receptor blockade, heart failure therapy, left ventricular reverse remodeling

Introduction

Despite numerous advances in therapy for cardiovascular disease, heart failure continues to be a major and growing public health concern. The prognosis for severe heart failure in the absence of medical intervention is grave, marked by progressive symptomatic deterioration and death.^{1,2}

Over the last decade, major trials have defined treatment strategies that improve the prognosis for patients with heart failure. Therapy with angiotensin-converting enzyme (ACE) inhibitors has improved both patient symptomatic status and survival in mild to severe heart failure.³⁻⁷ This clinical improvement has been associated with a partial arrest of the otherwise inevitable continued deterioration in left ventricular

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systolic function, resulting in stabilization of left ventricular end-diastolic size and ejection fraction.^{8,9}

The addition of beta-receptor blockade to heart failure therapy has allowed further improvement in symptomatic status over and above conventional dose ACE inhibitor therapy, resulting in a reduction in transplant requirement and/or in improved survival.¹⁰⁻¹² Of importance is the fact that beta-receptor blockade has actually led to a partial reversal of heart failure-associated deterioration in systolic function, achieving significant increases in left ventricular ejection fraction.^{13,14}

We have recently reported that high doses of ACE inhibitors in conjunction with nitrates may also reverse heart failure remodeling, increasing left ventricular ejection fraction while decreasing left ventricular size.^{15,16}

This study was designed to determine prospectively whether the addition of beta-receptor blocker therapy to high-dose ACE inhibitor-nitrate therapy has an additive impact on patient clinical status and left ventricular remodeling. We hypothesized that beta blockade added to high-dose ACE inhibitor-nitrates would further potentiate the reversal of heart failure.

Methods

Study Patients

All patients referred and followed with severe heart failure were prospectively entered into a heart failure database. Patients with unstable ischemic syndromes, severe obstructive valvular pathology, primary hypertrophic, restrictive, and infiltrative cardiomyopathies, pericardial constriction, severe hepatic, renal, and pulmonary end-organ disease were not entered. Patients in our program had echocardiographic follow-up routinely performed every 6 months.

We prospectively followed 13 sequential patients clinically and with echocardiographic studies at baseline, at 6 months while on maximal ACE inhibitor-nitrate therapy without beta blockade, and at 12 months following the addition of beta-receptor blocker therapy. Eight of these patients also had serial semiannual measurements of aerobic capacity. Each patient served as his/her own control.

To determine the impact of beta-receptor blockade with high-dose ACE inhibition in a larger patient cohort, we also retrospectively reviewed baseline and 12-month follow-up echocardiographic data on all database patients on >40 mg/day of lisinopril (*n* = 85), of whom 36 were receiving beta-receptor blocker therapy.

Medical Therapy

For the 13 patients, ACE inhibitor-nitrate therapy was intensified, as previously outlined, guided by hemodynamic response and findings on physical examination.¹⁶ Lisinopril was increasingly uptitrated in the presence of continued adequate systemic systolic arterial blood pressure (>90 mmHg) and preserved end-organ perfusion up to a maximal dose of

80 mg/day. Isosorbide dinitrate was initiated, and doses were increased to a maximal dose of 480 mg/day for any of the following conditions: continued symptomatic ischemia, elevation of right ventricular filling pressures per physical examination, pulmonary hypertension in excess of 40 mmHg, moderate to severe left ventricular chamber enlargement (≥ 6 cm left ventricular end-diastolic diameter), and/or moderate to severe mitral regurgitation as estimated on Doppler echocardiographic examination. Dose titration was limited in patients experiencing lightheadedness or other signs of intolerance, but was resumed after days to weeks of re-equilibration. For hypotensive patients with systolic arterial blood pressure <90 mmHg, diuretic dosages were carefully lowered to allow increases in vasodilator therapy. All patients were maintained on digitalis.

Beta-1 receptor blockade was initiated at 6 months following maximal intensification of lisinopril-nitrate therapy with atenolol at 6.25 mg/day, with upward dose titrations at 6.25 mg increments to a maximal dose of 50 mg twice daily. Dose increases were limited by reaching the target dose, by drug intolerance or side effects, by achieving relief of symptoms, or by reaching a resting heart rate of 55–65 beats/min.

Patient Follow-Up

Two-dimensional echocardiograms were obtained at baseline and semiannually. Echocardiographic measurements were made in a blinded fashion by staff echocardiographers not involved in the heart failure program. Mitral regurgitation was graded as follows: 1+ = mild, 2+ = mild/moderate, 3+ = moderate, and 4+ = severe.

In 8 of 13 patients, exercise aerobic capacity was determined semiannually in conjunction with echocardiography. The metabolic stress test employed a stationary bicycle protocol with load increments of 25 W every 3 min up to symptom-limiting maximal fatigue. A metabolic cart (Sensormedics, Yorba Linda, Calif.) was used to assess expired gases for oxygen consumption (VO_2) every 15 s.

Statistical Analysis

All 13 patients in this study spent at least 12 months in follow-up. Data are presented as mean $\pm$ standard deviation. Differences between group mean values were assessed with analysis of variance (StatView 4.1, Abacus Concepts, Inc., Berkeley, Calif.), and a Student-Newman-Keuls test. For dichotomous data, the chi-square test was used. Statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

Table I presents demographic and clinical characteristics at baseline for the 13 patients. Nine patients were Caucasian, and 10 were men. Twelve of the 13 patients had been referred for transplant consideration.

TABLE I Baseline characteristics of 13 patients with cardiomyopathy

Age (years)	52 ± 8
Sex (male/female)	10/3
Race (white/nonwhite)	9/4
New York Heart Association class	2.9 ± 0.7
Heart failure duration (years)	4.8 ± 2.2
Ischemic/nonischemic cardiomyopathy	2/11
Heavy alcohol use	0
Peripartum cardiomyopathy	0
Heart rate (min)	92 ± 18
Systemic systolic blood pressure (mmHg)	122 ± 27
Ejection fraction (%)	19 ± 8

Values are presented as mean ± standard deviation.

Medications

All patients were maintained on digoxin. Diuretics were discontinued in four patients. Lisinopril was uptitrated from 15 ± 13 to 53 ± 31 mg/day, isosorbide dinitrate from 19 ± 36 to 217 ± 213 mg/day. All patients tolerated the addition of beta blockade, with a final atenolol dose of 46 ± 23 mg/day.

Patient Clinical Status

In follow-up, no patient required intravenous inotropic support or heart transplant, and no patient died. As a group, New York Heart Association classification improved from 2.9 ± 0.7 at baseline to 1.8 ± 0.8 on lisinopril-nitrates ($p < 0.05$), to a final 1.5 ± 0.5 ($p = \text{NS}$) on beta blockade. Systolic arterial blood pressure remained unchanged over time. There was an overall significant decline in heart rate from baseline to 12 months ($p = 0.005$), decreasing from 91 ± 18 to 81 ± 17 on ACE inhibitor-nitrates alone, and to 71 ± 9 with beta blockade ($p = \text{NS}$). Heart failure-related hospitalizations per year overall decreased ($p = 0.002$), from 1.1 ± 0.9 to 0.5 ± 0.9 with vasodilator therapy only, and no patient required hospitalizations while on beta blockers ($p = \text{NS}$). For the eight patients who underwent assessment of exercise capacity, peak oxygen consumption tended to increase while on vasodilators

from an initial value of 17 ± 7 to 21 ± 5 ml O₂/kg/min ($p = 0.06$). No further change was observed while patients were on beta blockade (Table II).

Echocardiographic Findings

Ten of the 13 patients had an increase in left ventricular ejection fraction while on ACE inhibitor-nitrates alone, and 4 of 13 patients had a subsequent drop in ejection fraction while on beta blockade. For all patients, average ejection fraction changed from 19 ± 8 to 33 ± 14% at 6 months on ACE inhibitor-nitrates ($p = 0.005$), and to 36 ± 18% at 12 months on beta blockade ($p = \text{NS}$) (Fig. 1). This change was associated with an overall reduction in the severity of mitral regurgitation from 1.9 ± 1.4 to 0.6 ± 0.9 at 12 months ($p = 0.02$).

To determine whether the presence of beta-receptor blockade had any differential impact on left ventricular function with high-dose ACE inhibition, > 40 mg/day of lisinopril, in a larger group of patients, we retrospectively reviewed the echocardiographic findings at baseline and at 12 months for 85 patients on lisinopril 70 ± 16 mg/day, with 36 of the 85 patients on atenolol 54 ± 33 mg/day. For the group as a whole, left ventricular ejection fraction increased (19 ± 7 to 31 ± 6%, $p = 0.0005$) with a decline in the severity of mitral regurgitation (2.1 ± 1.3 to 1.2 ± 1.3, $p = 0.01$). However, both actual 12-month echocardiographic findings as well as calculated changes were not significantly different for patients in the presence or absence of beta-receptor blockade (Table III).

Discussion

We found that uptitration to high-dose ACE inhibitor-nitrate therapy effectively reversed the clinical severity of heart failure, improving symptomatic and functional status as well as left ventricular systolic function. The subsequent addition of beta blockade was well tolerated. Although symptoms and left ventricular systolic function tended to improve on beta blockade, these trends were statistically not significant and thus did not substantiate our hypothesis that the addition of beta blockers would significantly potentiate the clinical benefit of high-dose ACE inhibitor-nitrate therapy.

TABLE II Initial, 6 month, and 12 month clinical parameters

Clinical parameter	Initial	6 Months ACE inhibitor-nitrates alone	12 Months beta blocker added	p Value initial-12 months
Heart rate (n = 13)	91 ± 18	81 ± 17	71 ± 9	0.005
Systemic systolic blood pressure (mmHg) (n = 13)	122 ± 27	116 ± 18	121 ± 14	NS
Peak aerobic capacity (mlO ₂ /kg/min) (n = 8)	17 ± 7	21 ± 5	21 ± 8	0.06
Hospitalizations (n = 13)	1.1 ± 0.9	0.5 ± 0.9	0	0.002

The changes, initial to 6 months, 6 months to 12 months, were not separately statistically significant.

Abbreviations: ACE = angiotensin-converting enzyme, NS = not significant.

FIG. 1 All 13 patients underwent initial, 6-month, and 12-month follow-up echocardiography. 6 Months: ACE inhibitor-nitrates alone; 12 months: beta blocker added. The p value (6–12 months) was not significant. ACE = angiotensin-converting enzyme, LV = left ventricular. ■ = Initial, ■ = 6 months, ■ = 12 months.

Impact of High-Dose Angiotensin-Converting Enzyme Inhibitor-Nitrates

We have previously shown that high-dose ACE inhibitor and nitrate therapy may not only stabilize but actually reverse the heart failure remodeling process.¹⁶ Correspondingly, there was a significant improvement in left ventricular ejection fraction over 6 months in response to uptitrated ACE inhibitor-nitrate therapy alone, associated with a significant lessening of the severity of functional mitral regurgitation.^{17–19}

Although moderate dose ACE inhibition (15–20 mg/day of enalapril)^{3,5,6} improves symptomatic status and survival of patients with mild to severe heart failure,^{3–7} this dosage range suffices only to stabilize left ventricular systolic dysfunction.^{8,9,20} It appears that at the higher dosages, pharmacologic mechanisms over and above hemodynamic unloading effects^{21–23} may be playing a role. The expected reduction in tissue angiotensin II production and endothelin expression,^{24,25} enhanced bradykinin-mediated generation of prostaglandin and nitric oxide would impact favorably on the regression of myocyte hypertrophy, on interstitial fibrosis, and myocyte metabolism.^{26–30}

Beta-Receptor Blocker Addition to High-Dose Angiotensin-Converting Enzyme Inhibitor-Nitrates

Beta-adrenergic blockade may improve myocardial metabolism in heart failure while protecting the myocardium from excessive catecholamine exposure.^{13,14,31–34} The postulated mechanisms of beta-blocker therapy would thus further complement and potentially enhance the expected effects of ACE inhibitor-nitrate therapy. A reversal of heart failure remodeling has been observed in numerous studies of beta-receptor blockade added to the lower dose range of ACE inhibition.^{10–14} However, when added to established high-dose ACE inhibitor-nitrates, atenolol therapy accomplished no further significant improvement in either functional status or left ventricular function. Neither did the presence of beta-receptor blockade significantly affect left ventricular recovery in the larger retrospective reference cohort.

TABLE III Retrospective 12-month echocardiographic changes on 85 patients in the presence or absence of atenolol

	⊕ Atenolol n = 36	– Atenolol n = 49	p Value
Ejection fraction (%)	⊕ 15 ± 14	⊕ 11 ± 13	NS
Left ventricular end-diastolic diameter (cm)	–0.4 ± 1	–0.2 ± 0.8	NS
Mitral regurgitation (0 = none, 4 = severe)	–0.9 ± 1.4	–0.8 ± 1.2	NS

Lisinopril dose: 70 ± 16 mg/day; isosorbide dinitrate dose: 248 ± 164 mg/day; atenolol dose: 54 ± 33 mg/day.

Abbreviation: NS = not significant.

It is likely that the failure to demonstrate additional changes with atenolol is due to the clinical and echocardiographic improvements already achieved by the group. That the cohort does not represent a “responder” selection bias is demonstrated by comparable findings in the larger retrospective cohort comprising all patients on high-dose ACE inhibitor-nitrates.

It would, however, appear that pharmacologic approaches to reverse ventricular remodeling, albeit complementary, may not be additive. Undoubtedly, the tissue remodeling process may induce a number of irreversible changes. Alternatively, even beta-receptor blockade in conjunction with high-dose ACE inhibitors and nitrates may not yet comprehensively control all the auto- and paracrine neurohormonal and cytokine tissue effects of heart failure.^{35,36} Whether nonselective beta blockers or newer beta blockers with vasodilator properties offer an advantage over earlier selective beta-1 receptor blockers is currently being studied. Conceivably, additional therapy targeting inflammatory cytokines, angiotensin II, and/or endothelin-1 receptors might further enhance the reversal process.

Study Limitations

Our study is not a randomized, placebo-controlled trial for the addition of beta-blocker therapy over and above high-dose lisinopril-nitrate therapy. The number of patients studied is small, and the observed changes at 12 months may actually reflect the continued response to ACE inhibitors-nitrates alone rather than the effect of added beta-blocker therapy.

On the other hand, there was a trend toward improvement seen with beta blockade, and a large cohort may have shown greater benefit. “Early” versus “late” addition of beta blockade, or a nonselective third generation beta-receptor blocker may have had different outcomes.

Conclusion

We found that high-dose ACE inhibitor-nitrate therapy lessened clinical heart failure-related symptoms and improved

functional status and left ventricular function. The addition of beta-receptor blockade to high-dose lisinopril-nitrates was well tolerated but did not significantly further enhance functional capacity or reverse the remodeling of heart failure. The potential for pharmacologic reversal of systolic dysfunction may be limited despite the use of complementary therapeutic modalities to impact comprehensively on neurohormonal mediators of heart failure remodeling. Larger randomized, placebo-controlled trials of beta-receptor blockade added to high-dose ACE inhibitor-nitrate therapy are needed to confirm these observations.

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