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Impact of Left Ventricular Size on Pharmacologic Reverse Remodeling in Heart Failure

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Summary

Background and hypothesis: Although medical therapy may normalize echocardiographic left ventricular (LV) systolic function in selected patients with cardiomyopathy, other patients experience no change or a further deterioration in heart failure remodeling. Our aim was to determine what clinical or echocardiographic parameters predict a beneficial therapeutic response.

Methods: We prospectively followed biannual clinical and echocardiographic assessments in 215 patients. Forty-six of these patients ("Nonresponders") experienced no change or a decline in LV ejection fraction at 6 months. Of the 148 patients who improved LV function, 21 ("Responders") normalized LV systolic function at 6 months. Only Responders (n = 21) and Nonresponders (n = 46) were compared.

Results: On average, these 67 patients were 54 ± 12 years old with 4.5 ± 3.3 years of heart failure. At 6 months, following uptitration of angiotensin-converting enzyme inhibitors and nitrates, Responder LV ejection fraction rose from 22 ± 6 to 50 ± 5% with improvement in New York Heart Association classification (2.6 ± 0.8 to 1.5 ± 0.8, p = 0.001). These patients had significantly more favorable clinical and echocardiographic outcomes versus Nonresponders despite comparable medical therapy. All baseline demographic, clinical, and echocardiographic variables were equivalent, except for initial LV end-diastolic diameter which differentiated Nonresponders (7.1 ± 0.7 cm) from Responders (6.1 ± 0.8 cm), p = 0.007.

Conclusion: Thus, although heart failure therapy improves LV systolic function in a majority of patients, with normalization in up to 10% of patients, significant LV enlargement may render remodeling unresponsive to pharmacologic intervention, with a potential future need for alternative mechanical or surgical intervention.

Key words: heart failure remodeling, angiotensin-converting enzyme inhibitors, nitrates, left ventricular size

Introduction

Heart failure is characterized by a gradual but inexorable decline in symptomatic and functional status, associated with progressive left ventricular (LV) dilation, increasing chamber sphericity, and growing functional incompetence of the atrioventricular valves.[1,2]

Although conventional-dose angiotensin-converting enzyme (ACE) inhibitor therapy improves heart failure symptomatology and patient prognosis,[3–6] this approach serves only to stabilize but not to reverse the remodeling process of heart failure.[7,8]

In contrast, beta-receptor blocker[9–12] as well as high-dose ACE inhibitor-nitrate therapy[13–15] in heart failure may not only stabilize but actually partially reverse the heart failure remodeling, significantly increasing resting LV ejection fraction with a reduction of LV chamber size in a majority of patients. In selected instances, such therapy may normalize resting LV systolic function in patients despite a longstanding history of heart failure.[13] In contrast, certain patients do not respond to therapy, with no change or with an actual deterioration of their echocardiographically determined adverse heart failure remodeling.

The aim of our study was, therefore, to determine what clinical or echocardiographic parameters may predict full reversal of heart failure remodeling with pharmacologic intervention, versus a lack of response, by comparing patients who had echocardiographically normalized cardiac function with pa-

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tients who had no change or a deterioration of echo-determined cardiac function.

Methods

Study Patients

All patients with well-established heart failure were prospectively entered into a database with retrospective data analysis. Patients with unstable ischemic syndromes; primary valvular pathology; primary hypertropic, restrictive, and infiltrative cardiomyopathies; pericardial diseases; as well as other significant end organ diseases were excluded from analysis. Patients in our program were followed with routine semiannual echocardiographic studies.

Of 215 patients with baseline resting LV ejection fraction ≤35%, who had at least two serial semiannual echocardiograms, 46 patients were identified who experienced no change or an actual decline of their LV ejection fraction at 6 months follow-up. These constituted our "Nonresponder" group. All the remaining 148 patients had some improvement in resting LV systolic function. However, 21 of 148 patients, termed "Responders" to medical therapy, nearly normalized LV systolic function at 6 months by attaining an ejection fraction of ≥45%. For purposes of this study, only Nonresponders (n = 46) and Responders (n = 21) were compared.

Medical Therapy

For all patients, ACE inhibitor-nitrate therapy was intensified as previously outlined. Lisinopril was uptitrated, as tolerated, to a maximum dose of 80 mg/day. Isosorbide mononitrate dosing was initiated and increased to a maximum of 240 mg/day. All patients received digitalis. Beta-receptor blockers, amiodarone, and diuretics were used on an as needed basis.

Follow-Up

Two-dimensional echocardiograms were obtained routinely at baseline and semiannually, with measurements made in blinded fashion by staff echocardiographers not involved in the follow-up of patients with failure. Mitral regurgitation severity was graded at 1 = mild, 2 = mild/moderate, 3 = moderate, 4 = severe.

Statistical Analysis

All patients in the study spent at least 6 months in follow-up. Data are presented as mean ± standard deviation. Differences between group mean values were assessed using analysis of variance (ANOVA) (STATVIEW 4.1, Abacus Concept, Inc., Berkeley, Calif.). For dichotomous data, chi-square test was used. Statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

Of the 67 patients, 51 were men, 46 were white, and 21 had ischemic cardiomyopathy. On average, patients were 54 ± 12 years old, with established heart failure for 4.5 ± 3.3 years. Presenting New York Heart Association (NYHA) class was 2.8 ± 0.8. Table I shows comparable demographic and clinical characteristics for Responders and Nonresponders.

Medications

All patients were maintained on digoxin. Lisinopril dosage was uptitrated from 17 ± 14 mg/day to 45 ± 26 mg/day and 39 ± 26 mg/day (p = NS) for Responders and Nonresponders, respectively. Isosorbide mononitrate was uptitrated to 97 ± 53

TABLE I Demographics and initial clinical and echocardiographic findings of Responders and Nonresponders

	Responders (n = 21)	Nonresponders (n = 46)	p Value
Age (years)	54 ± 12	53 ± 11	NS
Race (black/white)	9/12	12/34	NS
Sex (male/female)	17/4	34/12	NS
New York Heart Association class	2.6 ± 0.8	2.9 ± 0.8	NS
Heart failure duration (years)	4.3 ± 2.4	5.9 ± 3.4	NS
Etiology (nonischemic/ischemic)	17/4	29/17	NS
History of hypertension (yes/no)	9/12	10/36	NS
History of diabetes mellitus (yes/no)	2/19	9/37	NS
History of alcohol use (yes/no)	5/16	10/36	NS
Heart rate/min	87 ± 12	88 ± 15	NS
Systolic blood pressure (mmHg)	125 ± 21	114 ± 16	0.04
Ejection fraction (%)	22 ± 6	21 ± 7	NS
Mitral regurgitation severity (0 = none, 4 = severe)	2.0 ± 1.1	2.2 ± 1.3	NS
Left ventricular end-diastolic diameter (cm)	6.1 ± 0.8	7.1 ± 0.7	0.0007

Values are presented as mean ± standard deviation.
Abbreviation: NS = not significant.

TABLE II Six-month clinical and echocardiographic characteristics of Responders and Nonresponders

	Responders (n = 21)	Nonresponders (n = 46)	p Value
Systolic blood pressure (mmHg)	123 ± 21	108 ± 19	0.01
Heart rate/min	75 ± 11	77 ± 14	NS
New York Heart Association classification	1.5 ± 0.8	2.1 ± 0.9	0.02
Left ventricular ejection fraction (%)	50 ± 5	17 ± 6	N/A
Left ventricular end-diastolic diameter (cm)	5.4 ± 0.6	6.9 ± 0.8	<0.0001
Mitral regurgitation severity (1 = mild, 4 = severe)	0.7 ± 1.1	1.8 ± 1.4	0.004

Abbreviations: NS = not significant, N/A = not applicable, by cohort selection.

mg/day and 121 ± 83 mg/day, respectively (p = NS). Ninety percent of patients required diuretics, 21% of patients were on beta-receptor blocker therapy, and 12% were on amiodarone, with no significant user difference between Responders and Nonresponders.

Clinical Status and Echocardiographic Findings

Responders: By cohort selection, when compared with baseline, the 21 Responder patients experienced a significant improvement in echo-determined ejection fraction at 6 months. Specifically, LV ejection fraction increased from 22 ± 6 to 50 ± 5% (p = N/A). Correspondingly, LV end-diastolic diameter decreased from 6.1 ± 0.8 to 5.4 ± 0.6 cm (p = 0.003). The severity of functional mitral regurgitation improved from 2.0 ± 1.1 to 0.7 ± 1.1 (p = 0.005).

Responder patients improved symptomatically, NYHA classification changing from 2.6 ± 0.8 to 1.5 ± 0.8 (p = 0.001). This improvement in echocardiographic parameters occurred with no change in systolic blood pressure in follow-up, but with a reduction in resting heart rate from 87 ± 12 to 75 ± 11/min (p = 0.001).

Nonresponders: This group was selected to show no rise in LV ejection fraction, changing from 21 ± 7 to 17 ± 6% (p = N/A). Although LV end-diastolic diameter remained effectively unchanged at 7.1 ± 0.7 versus 6.9 ± 0.8 cm, there was some decline in the severity of functional mitral regurgitation in this group as well, from 2.2 ± 1.3 to 1.8 ± 1.4 (p = 0.01).

For Nonresponders, systemic blood pressure tended to fall in follow-up from 114 ± 16 to 108 ± 19 mmHg (p = 0.05). Heart rate also slowed in response to therapy from 88 ± 15 to 77 ± 14/min (p = 0.01), and patients experienced some improvement in symptomatic status, NYHA classification changing from 2.9 ± 0.8 to 2.1 ± 0.9 (p = 0.01).

For the entire group of 215 patients, there was no correlation between the reversal of the heart failure remodeling (as measured by change in ejection fraction, reduction in LV end-diastolic diameter, or degree of mitral regurgitation) and the initial LV end-diastolic diameter.

Table II contrasts the 6-month determinations of symptomatic, clinical, and echocardiographic parameters for Responders and Nonresponders. Responders had a higher follow-up systolic blood pressure and greater symptomatic improvement. The more favorable clinical and echocardiographic outcomes of Responders versus Nonresponders occurred with no significant differences in their medical therapy or use of beta-receptor blockade.

At baseline, both groups were demographically similar with no significant differences in age, duration of heart failure, etiology, history of hypertension, social alcohol use, diabetes, gender, or race. Both groups were similarly symptomatic with comparable impairment of baseline LV systolic function. Systemic blood pressure tended to be higher at baseline for Responders (Table I).

As shown in Figure 1, initial LV size, as determined by LV end-diastolic diameter, significantly differentiated between

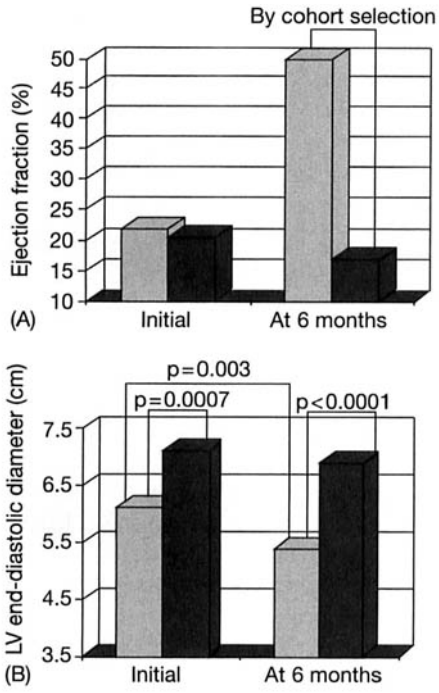

FIG. 1 Left ventricular (LV) ejection fraction (A) and end-diastolic diameter (B) for Responders and Nonresponders initially and at 6 months. Responders had significantly smaller initial LV size, which normalized in follow-up on medical therapy. ▨ = Responders, ■ = Nonresponders.

Responders and Nonresponders. Responders had an LV end-diastolic diameter of 6.1 ± 0.8 cm compared with Nonresponders who had a diameter of 7.1 ± 0.7 cm ($p = 0.0007$) (Table I).

Discussion

Beta-receptor blocker therapy has repeatedly been shown to achieve a partial reversal of heart failure-related remodeling.[9–12] High-dose ACE inhibition (32.5-35 mg/day of lisinopril) has recently been reported to impact beneficially on patient mortality and hospitalization, as combined secondary endpoints, in the Assessment of Treatment with Lisinopril and Survival (ATLAS) trial. We have previously found that ACE inhibitor-nitrate therapy, uptitrated from conventional doses to higher levels, in the absence of beta blockade, also reversed the remodeling of established, long-standing heart failure in a majority of patients.[13–15]

Although the majority of our patients (148 of 215) improved their echocardiographic function in follow-up,[13] 21 of 215 or 10% of patients with heart failure in our registry (Responders) actually normalized their LV function on intensified pharmacologic intervention at 6 months. In contrast, 46 of 215, or approximately 20% of patients (Nonresponders) continued to experience progressive deleterious heart failure remodeling despite similarly intensified therapy. It is of interest that even the Nonresponders (as defined by lack of improved systolic function) did demonstrate reduced mitral regurgitation on echocardiography; furthermore, these patients did improve symptomatically. Although the benefits of vasodilator therapy were attenuated, they were still present.

Responders tended to have higher systemic blood pressure, possibly suggestive of greater underlying contractile reserve that might respond to medical therapy.

Responders also had a significantly smaller LV size at baseline than did Nonresponders. We have previously observed that high-dose ACE inhibitor-nitrate therapy in heart failure reversed severe functional mitral insufficiency via reversal of remodeling only in those patients with LV end-diastolic size ≤ 6.8 cm.[16] Our findings in this group of patients complement that observation. It is noteworthy that only 29 of the 148 patients who had partial reversal of remodeling also had LV end-diastolic diameters ≥ 7.1 cm. Although heart failure remodeling improves with intensive medical therapy in a majority of patients, severe ventricular dilatation may be associated with irreversible interstitial and cellular changes that have become resistant to pharmacologic intervention.

Our findings support the need for early intensive pharmacologic therapy to impact on chamber remodeling, prior to irreversible dilation. On the other hand, patients with severe LV enlargement, if eligible, may ultimately need to be directed to alternative mechanical and surgical interventions.

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