Clinical Investigations

Reverse Remodeling in Heart Failure with Intensification of Vasodilator Therapy

T. BARRY LEVINE, M.D., ARLENE B. LEVINE, M.D., STEVEN J. KETHEYIAN, PH.D., BARBARA NARINS R.N., MICHAEL LESCH, M.D.

Henry Ford Heart and Vascular Institute, Detroit, Michigan, USA

Summary

Background: Heart failure therapy with beta-receptor blockade has been shown to effect a partial reversal of left ventricular (LV) remodeling in heart failure.

Hypothesis: We tested the hypothesis that, in the absence of beta blockade, upitration of angiotensin-converting enzyme (ACE) inhibitor and nitrate therapy over conventional dosages would improve symptoms as well as LV function in patients with severe heart failure.

Methods: For patients with nonischemic or ischemic cardiomyopathy, intensive high-dose angiotensin-converting enzyme inhibitor and nitrate therapy was uptitrated. Echocardiograms were obtained semiannually and evaluated in a blinded fashion. Of 99 patients in the study, aged 55 ± 13 years, with heart failure for 5.2 ± 3.1 years, 74 were men, 69 were Caucasian, and 34 had ischemic cardiomyopathy. The final dosage of enalapril was 40 ± 23 mg/day and of isosorbide dinitrate it was 153 ± 127 mg/day.

Results: Initial New York Heart Association classification improved from 2.8 ± 0.9 to 1.7 ± 0.9 ($p < 0.001$) in 2.7 years of follow-up. Of the 99 patients, 72 further improved their ejection fraction. For the whole group, ejection fraction increased from $21 \pm 9\%$ to $30 \pm 13\%$ in 6 months ($p < 0.001$), with a reduction in LV end-diastolic size from 6.6 ± 0.9 to 6.3 ± 1.0 cm ($p = 0.002$), and a decrease in the severity of mitral regurgitation from mild/moderate to only mild. Resting heart rate declined with no change over time in systemic systolic blood pressure. Final ejection fraction for nonischemic patients ($n = 65$) was $36 \pm 16\%$ versus $23 \pm 9\%$ for the ischemic population.

Conclusion: Upitration of high-dose ACE inhibitor and nitrate therapy to higher doses is well tolerated in severe heart failure, further improves both clinical status and LV systolic function, and is more effective in nonischemic than in ischemic cardiomyopathy.

Key words: heart failure, vasodilator therapy, angiotensin-converting enzyme inhibition, nitrates, ventricular remodeling, left ventricular systolic function

Introduction

The natural history of heart failure is one of gradual but continued deterioration in cardiac function manifested by increasing symptoms and worsening exercise tolerance. Following either significant ischemic, infectious, or inflammatory myocardial insults that impair left ventricular (LV) systolic function, a process of progressive ventricular dilatation is initiated,^{1–3} associated with increasing sphericity of the ventricular chambers.⁴ Incompetence of the atrioventricular valves and increased wall stress due to chamber dilatation further compromise ventricular systolic function leading to a vicious cycle of maladaptive remodeling changes and their clinical sequelae.⁵

Heart failure therapy with angiotensin-converting enzyme (ACE) inhibitors enhances symptomatic status and improves patient prognosis in mild to severe heart failure.^{6–8} Such therapy has successfully slowed the inevitable continued decline of LV systolic function by stabilizing LV size and ejection fraction.⁹

Beta-receptor-blocker therapy has been shown to effect a partial reversal of LV remodeling in heart failure. Numerous studies of beta-receptor-blocker therapy have shown moderate increases in LV ejection fraction with a decline in LV end-diastolic volume.^{10–12}

In a number of centers, heart failure-transplant programs, long frustrated by limited donor heart availability and long transplant wait lists, have placed less emphasis on mechanical assist devices as bridges to transplant while simultaneously developing medical regimens for the stabilization of “end stage” heart failure. Initially, this took the form of intravenous inotropic support. Increasingly, higher doses of ACE in-

Address for reprints:

T. Barry Levine, M.D.
Henry Ford Hospital
Heart Failure and Transplant Program
K-14 Cardiology
2799 W. Grand Boulevard
Detroit, MI 48202, USA

Received: June 4, 1997

Accepted: June 10, 1997

hibitors and high-dose nitrate therapy have been employed in the therapy of such patients.¹³ However, a systematic assessment of the impact of dosage increases of vasodilator therapy for the treatment of heart failure has not been reported.

Consequently, this study was designed to determine the impact of uptitration of combination ACE inhibitor and nitrate therapy over conventional dosages on clinical status and LV function in patients with chronic heart failure, in the absence of beta-receptor blockade or amiodarone therapy.

Methods

Study Patients

All patients referred to the Heart Failure and Transplant Program at Henry Ford Hospital for either heart failure management or transplant evaluation were entered prospectively in a database. However, patients with unstable ischemic syndromes; severe obstructive valvular pathology; primary restrictive, hypertrophic, infiltrative cardiomyopathies; pericardial disease; chronic debilitating systemic illnesses; and significant pulmonary, renal, or hepatic end-organ damage were excluded.

For all patients seen at follow-up after initial referral, repeat echocardiographic studies were routinely performed every 6

months, and serial sequential semiannual echocardiographic data were thus available in 181 patients.

Of 181 patients, 82 were maintained on vasodilator therapy in combination with beta-receptor blocker therapy and/or amiodarone antiarrhythmic therapy, and 99 were managed with vasodilator therapy alone. The comparable baseline and follow-up demographic, clinical, and echocardiographic characteristics of both groups are shown in Table I.

The latter group of 99 patients, maintained on vasodilator therapy in the absence of beta blockade or amiodarone, constitutes the study cohort for this analysis. Of these patients, 46 had at least three serial semiannual echocardiographic studies. The comparable clinical and echocardiographic outcomes for both groups rule out a significant selection bias to this analysis.

Medical Therapy

Our standardized approach for all patients referred to our service on conventional dose vasodilator therapy was the initial "maximal" intensification of medical pre- and afterload reducing therapy at the time of referral, regardless of the setting (in- or out-patient) of the consult. "Maximal" vasodilator therapy implied that patients could not tolerate any further upward dose titration due to symptomatic hypotension or end-organ hypoperfusion at that time. However, following days or

TABLE I Baseline characteristics and clinical outcome for 181 patients with cardiomyopathy

	Vasodilator therapy only (n = 99)	Vasodilator and beta blockade (n = 82)	p Value
Baseline characteristics			
Age (years)	55 ± 13	54 ± 13	NS
Sex (male/female)	74/25	50/32	NS
Race (white/nonwhite)	69/30	57/25	NS
NYHA class	2.8 ± 0.9	2.8 ± 0.8	NS
Heart failure duration (years)	5.2 ± 3.1	4.9 ± 3.0	NS
Ischemic cardiomyopathy	34	23	NS
Nonischemic cardiomyopathy	65	61	NS
Heavy alcohol use	2	2	NS
Peripartum cardiomyopathy	4	2	NS
Atrial fibrillation	7	12	NS
AICD	8	6	NS
Heart rate (min)	88 ± 14	88 ± 18	NS
Systemic systolic BP (mmHg)	115 ± 20	120 ± 21	NS
Echo ejection fraction (%)	21 ± 9	20 ± 9	NS
Dobutamine dependence	24	21	NS
Transplant referral	61	57	NS
Follow-up clinical outcome			
Dobutamine need, transplant, or death	22	14	0.8
NYHA class	1.7 ± 0.9	1.6 ± 0.7	NS
Final echo ejection fraction (%)	32 ± 15	34 ± 14	NS

Values are presented as mean ± standard deviation. "Vasodilator therapy only" comprises the cohort for this report.

Abbreviations: AICD = automatic implantable cardiac defibrillator, BP = blood pressure, NYHA = New York Heart Association, NS = not significant.

weeks of equilibration, vasodilator therapy was again continuously, albeit gradually, titrated upward to tolerance, defined by symptoms, clinical findings, and systolic blood pressure. It should be emphasized that the titration process over the first 6 months of follow-up was very gradual and labor-intensive. Patients were seen or contacted as frequently as twice weekly for adjustments in medications as patient response and drug tolerability were constantly reassessed.

All patients received digitalis and vasodilator agents. Diuretics were used only as needed and dosages were adjusted based on clinical assessment of volume status. For hypotensive patients with systemic systolic blood pressure < 90 mmHg, diuretics were lowered to allow increases in vasodilator therapy, even in the presence of clinically detected mild volume overload. Angiotensin-converting enzyme inhibitors were continually dosed upward in the presence of continued adequate systemic systolic arterial blood pressure (> 90 mmHg) and preserved end-organ perfusion, to a final maximal dose of 80 mg/day of enalapril. This dose (40 mg b.i.d.) was selected as comparable to the 100–150 mg t.i.d. of captopril that had previously been shown to be both clinically and hemodynamically effective.^{14, 15} Nitrates were only used for symptomatic ischemia or for decompensated biventricular heart failure despite the use of ACE inhibitors, digoxin, and diuretic therapy. Nitrates were titrated upward for continued angina, for continued elevation of right ventricular filling pressures as defined by neck vein distention, for pulmonary hypertension, and/or for continued moderately severe mitral regurgitation as estimated via echocardiographic Doppler examination, up to a final dose of isosorbide dinitrate of 480 mg/day. Dose titration of all vasodilators was limited by patients experiencing lightheadedness or other signs of intolerance.

For dobutamine-dependent patients, vasodilator therapy was similarly intensified. When feasible, dobutamine was tapered off very slowly at 1 µg/kg/min over days to weeks.

Patient Follow-Up

Outpatients were assessed initially at weekly to monthly intervals. Outpatients requiring continuous intravenous dobutamine therapy were seen weekly. Two-dimensional Doppler echocardiography was carried out at baseline and semiannually. Routine echocardiographic determinations were made in a blinded fashion by staff echocardiographers who had no involvement in the program. The severity of mitral regurgitation was graded as 1 = mild, 2 = mild/moderate, 3 = moderate, and 4 = severe.

Patients underwent intense dietary counseling for sodium restriction and weight loss if indicated. All patients, including dobutamine-dependent patients were expected to participate in formal cardiac rehabilitation or to pursue an ongoing regular stationary cycling or walking program 5 to 6 days a week.

Statistical Analysis

All patients in the study spent at least 6 months in the treatment program. Each patient served as his own control. All

data are presented as mean ± standard deviation. Differences between group mean values were assessed using Anova (StatView 4.1, Abacus Concepts, Inc., Berkeley, Calif.). For dichotomous data, the chi-square test was used. Statistical significance was defined as $p < 0.05$.

Results

Patient Characteristics

Of the 99 patients in the study, 74 were men, 69 were Caucasian, and 34 had ischemic cardiomyopathy. The patients, averaging 55 ± 13 years of age, had been diagnosed as having heart failure for 5.2 ± 3.1 years. Presenting New York Heart Association (NYHA) class severity was 2.8 ± 0.9 .

Of the 99 patients studied, 61 had been referred for transplant wait-listing, 24 had been treated with intravenous dobutamine prior to or at referral (Table I). During the 2.7 ± 2.0 year follow-up, 7 patients died, and 10 patients either underwent heart transplantation or were still actively awaiting transplant. Of the remaining patients, five were still intermittently in need of dobutamine inotropic support despite maximal vasodilator therapy.

Medical Regimen

All of the 99 patients included in this study were maintained on digoxin with diuretic dosages adjusted, usually downward, according to need (74%) as defined by volume status, prerenal azotemia, and the need to increase vasodilator doses. Of these, 97% were on ACE inhibitor therapy (18 ± 17 mg/day initial to 40 ± 23 mg/day final dose), with 76% in combination with isosorbide dinitrate therapy (31 ± 48 mg/day initial to 153 ± 127 mg/day final dose). No patients were on amiodarone therapy or beta-receptor blockade per cohort selection.

Clinical and Symptomatic Status

For the group as a whole, symptomatic status improved with a change in initial NYHA classification from 2.8 ± 0.9 to 1.7 ± 0.9 ($p < 0.0001$) in 2.7 years of follow-up. Heart rate declined from 88 ± 14 to 79 ± 14 ($p < 0.001$); however, systemic systolic blood pressure remained effectively unchanged, at 115 ± 20 mmHg initial versus 110 ± 18 mmHg final ($p = \text{NS}$).

Echocardiographic Findings

Of the 99 patients studied, 72 experienced an improvement in ejection fraction; for 27 patients there was no change or a decline. Table II characterizes the initial and 6-month follow-up echocardiographic parameters observed in all 99 patients. On intensified therapy, the patients experienced a further significant increase in ejection fraction from $21 \pm 9\%$ to $30 \pm 13\%$ ($p < 0.0001$). This change was associated with a reduction in LV end-diastolic size and a decrease in the severity of mitral regurgitation from mild/moderate severity to only mild. There

TABLE II Initial and 6-month echocardiographic parameters

Echo parameter	Initial (n = 99)	6 Month (n = 99)	p Value
LV ejection fraction (%)	21 ± 9	30 ± 13	<0.0001
LV end-diastolic diameter (cm)	6.6 ± 0.9	6.3 ± 1.0	0.002
Mitral regurgitation (1 = mild, 2 = mild-mod, 3 = moderate)	2.1 ± 1.3	1.4 ± 1.3	0.0002
Wall thickness (cm)	1.0 ± 0.2	1.1 ± 0.2	NS

Data are presented as mean value ± standard deviation. All 99 patients underwent initial and 6-month follow-up echocardiography.

Abbreviations: Echo = echocardiographic, LV = left ventricular, NS = not significant.

was a trend toward an increase of LV end-diastolic wall thickness. For 46 patients with ≥3 serial 6-monthly echocardiograms, these improvements were sustained in the long-term follow-up of 12–72 months (3.1 ± 1.9 years), with a further reduction in the severity of mitral regurgitation (1.9 ± 1.5 initial to 1.1 ± 1.3 final, $p = 0.01$).

Etiology of Heart Failure

Nonischemic cardiomyopathy was seen in 66% of patients. Changes in systolic function for patients with nonischemic etiology significantly exceeded the response of ischemic patients (Table III) although the presenting severity of the systolic dysfunction was similar for both groups with respect to ejection fraction, the severity of mitral regurgitation, and LV size. Final ejection fraction for nonischemic patients was $36 \pm 16\%$ versus $23 \pm 9\%$ for the ischemic population ($p = 0.006$). The groups did not differ with respect to demographics, heart failure duration, or intensity of therapy.

Discussion

Our results show that a very gradual but continued upward titration of intensive vasodilator therapy over conventionally used doses is tolerated by patients with severe heart failure, resulting in an improvement in clinical status with no significant change in systolic arterial blood pressure. Even in the absence of beta-receptor blockade, the clinical improvement effected by higher dose vasodilator therapy caused a significant slowing of heart rate. Higher vasodilator doses led to a further improvement of LV systolic function with a reduction in LV end-diastolic size and mitral regurgitation. This improvement was more prominent in patients with nonischemic cardiomyopathy.

Clinical Response

The clinical improvement observed in these patients occurred with no effective change in systemic blood pressure over time despite the up-titration of vasodilator agents. This would suggest that the effects of medication-induced lowering of afterload and systemic vascular resistance were compensated for by an increase in forward cardiac output, in part due to a reduction in mitral regurgitation.^{4, 16} Alternatively, therapy-induced neurohormonal activation might account for the continued maintenance of systemic pressures.¹⁷ Although norepinephrine levels were not followed in this group of patients as a whole, they had been routinely assayed in a subgroup of 60 patients who were on a transplant wait-list and were followed between 1990 and 1993. These patients, managed in analogous fashion, tended to have a decline in catecholamine levels on therapy.¹³

Patients also experienced a lowering of resting heart rate. The relative tachycardia seen in the setting of symptomatic heart failure is compensatory due to an impairment of systolic func-

TABLE III Initial, 6-month, and final echocardiographic parameters for ischemic and nonischemic etiology

Echo parameter	Nonischemic cardiomyopathy (n = 65)	Ischemic cardiomyopathy (n = 34)	p Value
LV ejection fraction			
Initial	21 ± 9	21 ± 8	NS
6 Month	31 ± 14	28 ± 11	NS
Final	36 ± 16	23 ± 9	0.006
LV end-diastolic diameter (cm)			
Initial	6.6 ± 0.9	6.6 ± 0.9	NS
6 Month	6.2 ± 1.0	6.6 ± 0.9	0.09
Final	5.9 ± 1.0	6.5 ± 1.1	0.1
Mitral regurgitation (1 = mild, 2 = mild-moderate, 3 = moderate)			
Initial	2.1 ± 1.3	2.3 ± 1.2	NS
6 Month	1.4 ± 1.3	1.6 ± 1.3	NS
Final	1.1 ± 1.3	1.2 ± 1.4	NS

Data are presented as mean value ± standard deviation. "Final" represents the findings after 3.1 ± 1.9 years.

Abbreviations as in Table II.

tion, with increased neurohormonal activation and withdrawal of vagal tone.¹⁸ Improvement in cardiac function with intensive ACE inhibitor therapy would be expected to lead to a slowing of resting heart rate, as previously described.^{18, 19}

Echo Results and Analysis of Left Ventricular Function

The observed improvement in systolic function, specifically the rise in ejection fraction in conjunction with a fall in end-diastolic diameter in the absence of any significant change in systemic systolic blood pressure over time, may suggest a primary improvement in ventricular systolic performance. Improvements in systolic function have been documented in studies with carvedilol and bucindolol over the course of 3 to 6 months.^{10, 11}

We also found a significant lessening of the severity of mitral regurgitation. Mitral regurgitation occurs in heart failure as a result of an increase in chamber size and chamber sphericity.⁴ The observed decrement in mitral regurgitation severity independently reflects the reversal of the adverse remodeling process.¹⁶

Potential Mechanisms

Angiotensin-converting enzyme inhibition in heart failure has been primarily associated with significant improvements in survival for patients with moderate to severe heart failure.⁶⁻⁸ However, the effects of such therapy on heart failure remodeling have been less striking. In a dog model of heart failure, ACE inhibitor therapy resulted in stabilization of LV size and ejection fraction.²⁰ Similar results were observed in the SOLVD treatment arm,^{9, 21} with stabilization of LV end-diastolic diameter and at most minor improvements in ejection fraction on therapy.

Short-term studies of nitrate therapy post myocardial infarction have shown beneficial hemodynamic effects with increases in ejection fraction.²² Nitrates in conjunction with hydralazine have been associated with a small increase in ejection fraction²³ exceeding the changes found with enalapril.⁸ However, nitrates, although commonly used in heart failure therapy, have not previously been studied at high doses in combination with ACE inhibition.

The improvement in LV function observed in our patients exceeds changes previously observed for therapy with either ACE inhibitors or nitrates, and matches the observations with beta-receptor blockade.¹⁰⁻¹² What differentiates this study from prior vasodilator studies may be the combination of agents as well as the significantly higher dosages used. In contrast to the final medication dosages in our group of patients, prior studies have only employed moderate daily doses of ACE inhibitors, comparable to our patients' initial therapy, specifically 20 mg/day of enalapril for CONSENSUS,⁶ and 17 mg a day of enalapril for SOLVD.⁷ The improvements in ventricular function are likely multifactorial, encompassing the effects of both decreased load and mitral regurgitation. Although both pre- and afterload of the impaired ventricles were undoubtedly lowered by therapy,¹⁴ the lack of a signifi-

cant decline in systemic blood pressure over time suggests that changes in ventricular function occurred not solely in response to hemodynamics.

The medical regimen utilized may have affected cardiac autocrine and paracrine homeostasis. Angiotensin-converting enzyme inhibitor therapy lowers tissue angiotensin-II production with a reduction in the expression of endothelin-1,²⁴ resulting in a lessened stimulus for myocardial collagen deposition with impairment of oxygen delivery.²⁵ The associated inhibition of endothelium-based kininase may increase bradykinin to further arrest the stimulus for left ventricular hypertrophy and remodeling with beneficial vascular effects.²⁶ Heart failure has been associated with increased cytokine generation with negative inotropy mediated directly or indirectly.²⁷ In one study,²⁸ the beneficial beta-blocker effect on LV function has been associated with an improvement in cytokine expression. Whether this mechanism is directly due to beta blockade or whether it may play a role with other therapeutic modalities remains to be determined.

Nitrate Tolerance

High dosage nitrate therapy employed in conjunction with appropriate dosing intervals may have modulated the development of nitrate tolerance in this patient population. The unloading effects of nitrates in conjunction with their role as nitric oxide donors²⁹ would alleviate ischemia, mitigate the effects of local vasoconstrictor and mitogenic factors, and would clearly complement high-dose ACE inhibitor therapy as seen in infarct-healing models.³⁰

Nonischemic Versus Ischemic Cardiomyopathy

The tissue effect of combination therapy on reversibly injured myocytes may explain the striking differential response of nonischemic versus ischemic cardiomyopathy, which has also been seen with beta-receptor-blocker therapy.¹² The differential response to therapy may define nonischemic cardiomyopathy as a disease entity pathophysiologically distinct from ischemic cardiomyopathy, and the implication of this distinction may need to be more clearly defined in larger long-term studies. Whether the addition of beta-receptor-blocker therapy will further impact on the improvements achieved by high-dose vasodilators alone remains to be determined.

Study Limitations

The major weakness of the present study is that it is not a randomized, placebo-controlled trial for either high- or intermediate- versus low-dose ACE inhibition stratified for nitrate therapy. Left ventricular volumes or mass were not determined. However, this is a large cohort of patients, with each patient acting as his own control. Echocardiographic determinations were made in a blinded fashion. Comparable clinical and echocardiographic outcomes of patients in the study cohort with excluded patients on beta-receptor blockade (Table I) argue against a significant selection bias. Since patients

with significant end-organ disease were excluded from data analysis, it is conceivable that those with significant renovascular or peripheral vascular disease could be harmed by the high doses administered.

Conclusion

We have found that uptitration of vasodilator therapy over conventional dosages, employing angiotensin-converting enzyme inhibition in conjunction with nitrate therapy, is well tolerated in severe heart failure and leads to further improvement of symptomatic and clinical status. These higher vasodilator doses reverse the remodeling of heart failure and further improve left ventricular systolic function even in the population with end-stage heart failure that is referred for transplant. This improvement was found to be significantly more prominent in patients with nonischemic than in those with ischemic cardiomyopathy.

References

- Cohn JN: Structural basis for heart failure: Ventricular remodeling and its pharmacological inhibition. *Circulation* 1995;91:2504-2507
- Pfeffer MA, Braunwald E: Ventricular remodeling after myocardial infarction: Experimental observations and clinical implication. *Circulation* 1990;81:1161-1172
- Olivetti G, Capasso JM, Sonnenblick EH, Anversa P: Side to side slippage of myocytes participates in ventricular remodeling acutely after myocardial infarction in rats. *Circ Res* 1990;67:23-34
- Sabbah HN, Kono T, Rosman H, Jafri S, Stein PD, Goldstein S: Left ventricular shape: A factor in the etiology of functional mitral regurgitation in heart failure. *Am Heart J* 1992;123:961-966
- Cintron G, Johnson G, Francis G, Cobb F, Cohn JN: Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. *Circulation* 1993;87(suppl VI):7-23
- The CONSENSUS Trial Study Group: Effects of enalapril on mortality in severe congestive heart failure: Results of the cooperative North Scandinavian Enalapril Survival Study. *N Engl J Med* 1987;316:1429-1435
- The SOLVD Investigators: Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med* 1991;325:293-302
- Cohn JN, Johnson G, Ziesche S, Cobb F, Francis G, Tristani F, Smith R, Dunkman WB, Loeb H, Wong M: A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. *N Engl J Med* 1991;325:303-310
- Konstam MA, Rousseau MF, Kronenberg MW, Udelson JE, Melin J, Stewart D, Dolan N, Edens TR, Ahn S, Kinan D: Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of ventricular dysfunction in patients with heart failure. *Circulation* 1992;86:431-438
- Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR: Carvedilol improves left ventricular function and symptoms in chronic heart failure: A double-blind randomized study. *J Am Coll Cardiol* 1995;25:1225-1231
- Eichhorn EJ, Bedotto JB, Malloy CR, Hatfield BA, Deitchman D, Brown M, Willard JE, Grayburn PA: Effect of beta-adrenergic blockage on myocardial function and energetics in congestive heart failure: Improvements in hemodynamic, contractile, and diastolic performance with bucindolol. *Circulation* 1990;82:473-483
- Woodley SL, Gilbert EM, Anderson JL, O'Connell JB, Deitchman D, Yanowitz FG, Mealey PC, Volkman K, Renlund DG, Menlove R, Bristow MR: Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. *Circulation* 1991;84:2426-2441
- Levine TB, Levine AB, Goldberg AD, Narins B, Goldstein S, Lesch M: Reversal of end-stage heart failure is predicted by long-term therapeutic response rather than initial hemodynamic and neurohormonal profile. *J Heart Lung Transplant* 1996;15:297-303
- Levine TB, Franciosa JA, Cohn JN: Acute and long-term response to an oral converting-enzyme inhibitor, captopril, in congestive heart failure. *Circulation* 1980;62:35-41
- The Captopril Multicenter Group: A placebo-controlled trial of captopril in refractory chronic congestive heart failure. *J Am Coll Cardiol* 1983;2(4):755-763
- Hamilton MA, Stevenson LW, Child JS, Moriguchi JD, Walden J, Woo M: Sustained reduction in valvular regurgitation and atrial volumes with tailored vasodilator therapy in advanced congestive heart failure secondary to dilated (ischemic or idiopathic) cardiomyopathy. *Am J Cardiol* 1991;67(4):259-263
- Olivari MT, Carlyle PF, Levine TB, Cohn JN: Hemodynamic and hormonal response to transdermal nitroglycerin in normal subjects and in patients with congestive heart failure. *J Am Coll Cardiol* 1983;2:872-878
- Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN: Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relationship to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49:1659-1666
- Levine TB, Cohn JN: Determinants of acute and long-term response to converting enzyme inhibitors in congestive failure. *Am Heart J* 1982;104:1159-1164
- Sabbah HN, Shimoyama H, Kono T, Gupta RS, Sharov VG, Scicli G, Levine TB, Goldstein S: Effects of long-term monotherapy with enalapril, metoprolol and digoxin on the progression of left ventricular dysfunction and dilation in dogs with reduced ejection fraction. *Circulation* 1994;89:2852-2859
- Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, Shelton B, for the SOLVD Investigators: Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD Echocardiography Substudy. *Circulation* 1995;91:2573-2581
- Jugdutt BI: Effect of nitrates on myocardial remodeling after acute myocardial infarction. *Am J Cardiol* 1996;77:17C-23C
- Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH: Effect of vasodilator therapy on mortality in chronic congestive heart failure: Results of a Veterans Administration Cooperative Study. *N Engl J Med* 1986;314:1547-1552
- Sung CP, Arleth AJ, Storer BL, Olstein EH: Angiotensin type I receptors mediate smooth muscle proliferation and endothelin biosynthesis in rat vascular smooth muscle cells. *J Pharmacol Exp Ther* 1995;271:429-437
- Sabbah HN, Sharov VG, Cook JM, Shimoyama H, Lesch M, Goldstein S: Enalapril but not metoprolol improves capillary density and oxygen diffusion distance in left ventricular myocardium of dogs with moderate heart failure. *J Am Coll Cardiol* 1996;27:713-714
- Schorr K: Converting enzyme inhibitors and the interaction between kinins and eicosanoids. *J Cardiovasc Pharmacol* 1990;15(suppl 6):S60-68
- Habib FM, Springall DR, Davies GJ, Oakley CM, Yacoub MH, Polak JM: Tumor necrosis factor and inducible nitric oxide synthase in dilated cardiomyopathy. *Lancet* 1996;347:1151-1155
- Maisel AS: Beneficial effects of metoprolol treatment in congestive heart failure. Reversal of sympathetic-induced alterations of immunologic function. *Circulation* 1994;90:1774-1780
- Kelly RA, Smith TW: Nitric oxide and nitrovasodilators: Similarities, differences, and interactions. *Am J Cardiol* 1996;77:2C-7C
- Jugdutt BI, Khan MI, Jugdutt SJ, Blinston GE: Combined captopril and isosorbide dinitrate during healing after myocardial infarction: Effect on ventricular remodeling, function, mass and collagen. *J Am Coll Cardiol* 1995;25:1089-1096