ERIC J. EICHHORN, MD
Department of Internal Medicine (Cardiology Division), the University of Texas Southwestern and Dallas VA Medical Centers, Dallas, Texas

Our new understanding of heart failure: The role of beta-blockers in treatment

ABSTRACT

Beta-blockers, long considered contraindicated in heart failure, improve left ventricular function in this disease by improving the biology of cardiac myocytes. Whether they improve survival remains to be determined.

KEY POINTS

Heart failure is a downward spiral, in which impaired ventricular dysfunction elicits a cascade of compensatory mechanisms, including activation of the sympathetic nervous system, the renin-angiotensin system, and a variety of neurohormones. These compensatory mechanisms improve cardiac function in the short term, but worsen it over the long term.

Inotropic agents and some vasodilators can accelerate the pathophysiologic process of heart failure.

Recent findings indicate that beta-blockers, used with angiotensin-converting enzyme inhibitors, blunt the damaging effects of these compensatory mechanisms, improving the biology of cardiac myocytes and preserving ventricular function.

Candidates for beta-blocker therapy should be in stable condition, in class II or III heart failure.

The initial dosage should be very low and increased gradually, with vigilance for signs of cardiac decompensation.

FOR A LONG TIME, cardiologists viewed chronic heart failure as essentially pump failure—a syndrome of abnormal hemodynamics and cardiac reserve resulting in shortness of breath, fatigue and inability to exercise. In line with this thinking, treatment emphasized drugs such as inotropes to improve contractility, and vasodilators and diuretics to reduce load,[1] all with the goal of improving resting hemodynamics and exercise tolerance. By pharmacologically manipulating these hemodynamic measures, we hoped to improve outcome.

In the short term, these drugs seemed to work.[2–8] For a time patients could walk farther and faster, and reported having a better quality of life. Unfortunately, in the long term, these same drugs did not improve patient survival and in some cases actually decreased the survival rate.[9–13] The reason for this lack of long-term improvement is that inotropes and vasodilators did not improve the underlying abnormal biologic processes that damage cardiac myocytes as heart failure progresses. In fact, inotropes actually exacerbate these processes.[14]

The understanding of heart failure began to change in the late 1980s, when researchers discovered that angiotensin-converting enzyme (ACE) inhibitors decrease preload and afterload, increase exercise tolerance, stop ventricular remodeling, and increase the survival rate in patients with heart failure.[15–25] The reason for these improvements, as we are now finding out, is that ACE inhibitors improve the underlying biological processes affecting the myocytes.

In the last few years, we have found that beta-blockers can also improve the biology of

the cardiac myocyte, especially when combined with an ACE inhibitor.[14] And in the next few years, we will discover whether the biological benefits of this therapy will translate into prolonged survival.

WHY HEART FAILURE PROGRESSES

Imagine a patient with asymptomatic heart failure and an ejection fraction of 40%. Four years later, his ejection fraction has decreased to 20%, and he is in class III heart failure on the New York Heart Association (NYHA) scale. Yet he suffered no event such as a myocardial infarction in the intervening years. What happened?

Response to cardiac injury signals pathologic growth and remodeling

When a normal heart sustains an initial insult (due to a myocardial infarction, myocarditis, long-standing valvular heart disease or hypertension, or some unknown reason), the resulting left ventricular dysfunction activates several compensatory mechanisms[14]:

- Elevated preload stretches the myocytes, activating tissue-level factors such as angiotensin II[26] and atrial natriuretic factor.[27]
- Decreased blood flow in the aorta alters baroreceptor sensitivity, which deinhibits the sympathetic nervous system, leading to prolonged sympathetic nervous system arousal.[28]
- The renin-angiotensin system and sympathetic nervous system cross-activate each other: release of angiotensin II stimulates presynaptic norepinephrine release,[29,30] and stimulation of beta-1 receptors in the kidney stimulates renin release[31];
- Other neurohormones, including cytokines (tumor necrosis factor-alpha, interleukin-6),[32,33] endothelins,[34–36] and peptide growth factors[37–39] may also be activated by the failing heart.

Thus, in the short term, the sympathetic nervous system and the renin-angiotensin system compensate for a failing heart by constricting blood vessels to maintain blood pressure, increasing heart rate and contractility, and increasing preload to augment stroke volume by a Frank-Starling mechanism.[14,40,41] Unfortunately, over the long term, all of these factors also act as growth signals to the failing heart, triggering a process of pathological growth and remodeling.[14]

In response to growth signals, heart cells grow abnormally

The adult myocyte is terminally differentiated and so cannot enter the cell cycle and divide.[42,43] Thus, when it receives growth signals, it can only do one of two things: grow abnormally or die by apoptosis.[14,42]

Failing myocytes grow by constructing sarcomeres in series rather than in parallel.[44,45] Thus, they elongate, and as they do they change the size and shape of the left ventricle from small and elliptical to large and more spherical (FIGURE 1).[46,47]

Failing hearts need more oxygen but get less, leading to ischemia

The change in ventricular geometry increases the stress on the ventricular wall.[48] In turn, the elevation in wall stress leads to an increase in heart rate by sympathetic nervous system stimulation, which in turn leads to an increase in myocardial oxygen consumption.[49,50]

The failing heart also needs more oxygen because the myocytes are becoming less efficient in their use of energy. When myocytes grow pathologically, their ratio of myofibrils to mitochondria increases.[51] In addition, sympathetic nervous system stimulation causes a shift from using carbohydrates (which are efficient fuels) to free fatty acids (which are less efficient).[52]

Another reason these myocytes are less efficient is that as they are stimulated to grow, yet are unable to produce new cells, their genetic coding to produce fetal-like proteins is turned back on. Thus, instead of producing adult forms of myosin (alpha isoforms) to contract and relax the heart muscle, they produce a slower, less-efficient form (beta isoforms).[53] They may also produce other fetal products such as atrial natriuretic peptide and skeletal alpha actin.[26,27,54,55] Experiments in animals suggest that these myocytes also down-regulate their production of calcium-controlling proteins such as sarcoplasmic reticulum calcium ATPase,[55–57] although this has not been definitively shown in humans.

The sympathetic nervous system, renin, cytokines, and endothelins all promote abnormal cardiac remodeling

All of these changes further impair ventricular function, leading to a vicious cycle of further neurohormonal activation. Yet, at the same time that the damaged heart needs more oxygen than before, it receives less, due to other processes that limit oxygen delivery to the myocytes. To begin, the large spherical heart is less efficient as a pump; therefore, the coronary perfusion pressure is lower. In addition, the ventricular diastolic pressure is higher. Both of these factors reduce the blood flow to the myocytes.[58]

On the cellular level, angiotensin II stimulates fibroblasts, resulting in an increase in interstitial fibrosis and a change in the skeletal structure of the heart.[59,60] This process increases the distance that oxygen must travel as it diffuses from the capillaries to the myocytes, reducing the amount of oxygen reaching the myocytes.[61–63]

The failing heart thus becomes energy-depleted and can become ischemic, especially in the subendocardium, leading to cell injury and necrosis. Cell necrosis also appears to occur as an end result of direct exposure to norepinephrine[64] and angiotensin II.[65] This process may lead to more myocardial dysfunction.

ACE inhibitors plus beta-blockers reverse cardiac remodeling

Apoptosis

Although myocytes can die by the ischemic process described above, they can also die by apoptosis, a noninflammatory process that has been shown to occur in humans with dilated cardiomyopathy. Apoptosis may be mediated by a variety of factors such as tumor necrosis factor, transforming growth factor-beta, binding of the Fas ligand to the Fas receptor, calcium overload, activation of tumor suppressor genes (such as p53), or an increase in free radicals and oxidants, all of which are increased in the failing heart.[66] The resulting progressive cell death may also lead to a vicious cycle of worsening ventricular function and further up-regulation of neurohormones.[14]

INOTROPIC TREATMENT CAN ACCELERATE HEART FAILURE

Inotropic agents and some vasodilators can stimulate arrhythmias[9,10,67] and further neurohormonal activation[68,69] in patients with heart failure. Their use may lead to better hemodynamic measures in the short term, but a greater chance of dying in the long term as they accelerate the pathophysiologic process of heart failure.

In contrast, ACE inhibitors and beta-blockers reduce these growth-stimulating signals to the heart,[14] blocking and even in some cases reversing pathological growth.[14,21,22,70] ACE inhibitors by themselves attenuate abnormal growth,[14,21,22] but do not reverse the process, in part because the sympathetic nervous system continues to be activated over time.[71] Consequently, ACE inhibitors have a modest effect on survival.

BETA-BLOCKERS IMPROVE CARDIAC FUNCTION

More than 15 placebo-controlled studies involving more than 2,000 patients with chronic heart failure due to systolic dysfunction have examined the effect of beta-blockers on ventricular function.[52,72–91] Every study that lasted more than 1 month consistently showed that the left ventricular ejection fraction increases with beta-blocker therapy.

Ventricular function is improved

Most important, three human studies[52,82,92] and one animal study,[93] using four different beta-blockers, showed that the improvement in ventricular function is due to increased systolic ventricular performance. Improved performance appears to be due to enhanced contractility.[93] Not only does ventricular function improve, but myocardial oxygen consumption—the cost of doing work—does not increase.[52] This means that this therapy improves the mechanical and energy efficiency of the heart.

The improvement in ventricular function appears to be due to a biological effect on the myocytes.[14,94] Evidence for this comes in part from an echocardiographic study showing that the left ventricular ejection fraction does not increase at all during the first month of beta-blocker therapy.[70] Rather, the improvement appears to occur between 1 and 3 months, suggesting a late biological effect. In addition, a recent study demonstrated that as left ventricular function improved, myocyte proteins

How an injury to the heart causes ventricular dysfuncion

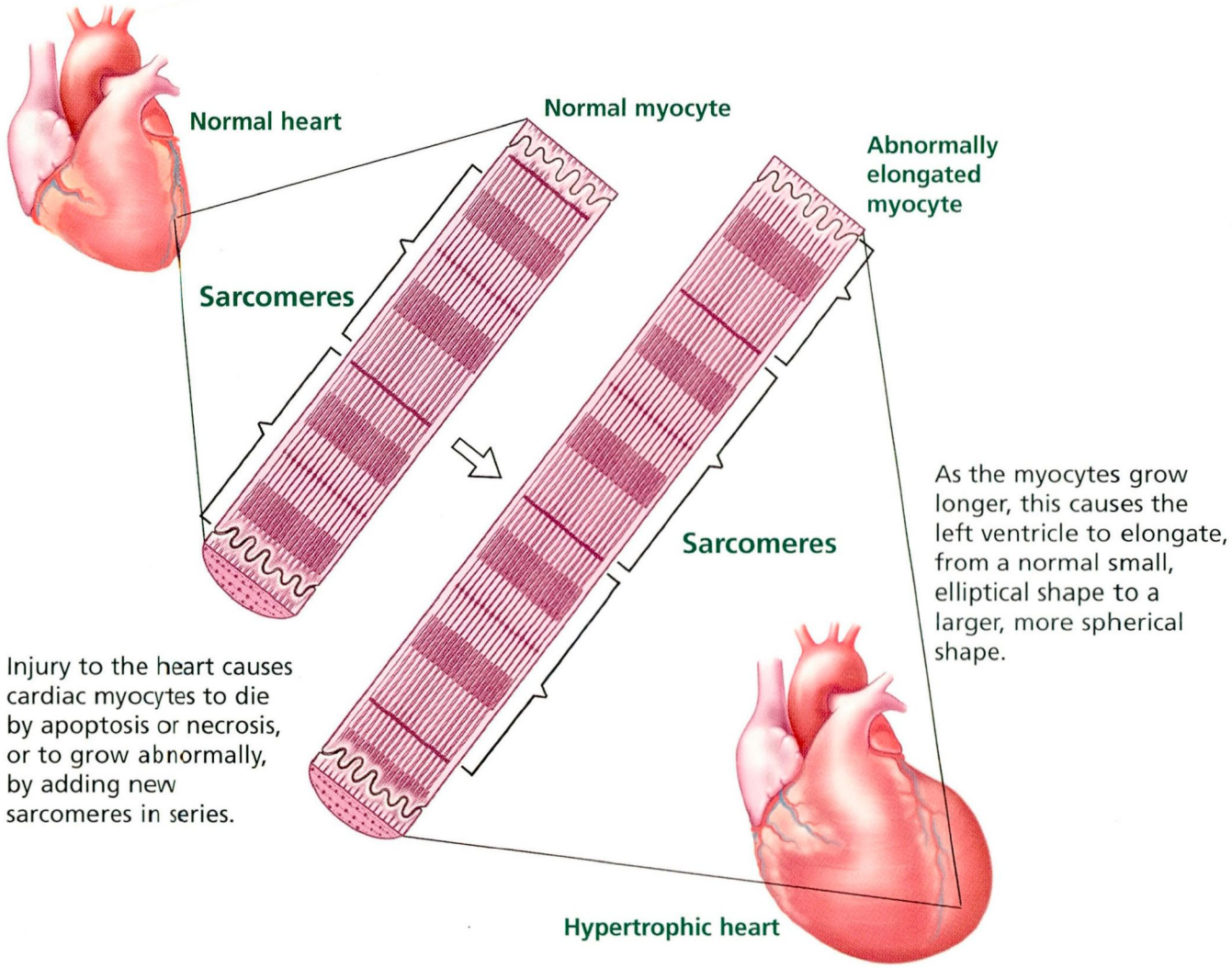

FIGURE 1

changed from slow beta-myosin heavy chains to the faster, adult alpha-myosin isoform.[94]

Pathologic ventricular remodeling is reversed

Long-term echocardiographic studies have demonstrated that left ventricular mass and volume decrease in response to beta-blocker therapy, and the shape of the ventricle changes from spherical to elliptical.[70,95] This suggests that beta-blockers, when added to ACE inhibitors, may reverse the remodeling of the failing ventricle, more evidence of a beneficial biological effect.

Exercise tolerance: mixed results

Exercise tolerance increased with beta-blocker therapy in some studies,[72,76,78–80,83–85] but not in others.[75,77,81,82,86–88] Because beta-blockers block the normal increase in heart rate and contractility that occurs in response to exercise (and to norepinephrine spillover during exercise), it is difficult to demonstrate a normalized response to exercise with beta-

blockers on board. However, in placebo-controlled studies, patients taking beta-blockers generally felt better and were better able to perform their daily activities.

Exercise tolerance tends to improve slightly with selective second-generation agents such as metoprolol, atenolol, and bisoprolol, but not with nonselective third-generation agents such as bucindolol, labetalol, and carvedilol.[96] The reason may be that second-generation agents cause less adrenergic blockade, allowing some increase in heart rate and contractility with exercise.[96]

DO BETA-BLOCKERS REDUCE MORTALITY?

Information from two databases suggest (but do not prove) that beta-blockers will reduce mortality in heart failure.[89,97]

The CIBIS trial[89] examined the effect of bisoprolol on survival in patients with NYHA class III and IV heart failure. The mortality rate was 20% lower in the group receiving bisoprolol than in those receiving placebo, but this trend did not reach statistical significance because the trial was too small.

Titration of beta-blockers may take months, especially in very ill patients

Four US trials[97] examined exercise capacity and progression of heart failure with the third-generation, nonselective agent carvedilol. These trials failed to demonstrate an improvement in exercise capacity,[87,88] but when the trials were put together and examined by a common data and safety monitoring board, a 65% reduction in all-cause mortality was observed.

The US trials were not designed to examine mortality, had an open-label period prior to randomization (which may have created a selection bias), were too short in follow-up, and had too few events to definitively state that carvedilol reduces mortality. However, the data are highly suggestive. In addition, all four trials together demonstrated a reduction in mortality and hospitalization, and each individual trial was consistent in the direction of these results.

Two carvedilol trials that had longer follow-up, the Mild Heart Failure trial from the US Program[98] and the Australia-New Zealand trial,[86,99] both demonstrated in patients with primarily NYHA class I and II heart failure that carvedilol reduced the combined endpoint of mortality and all-cause hospitalization.

Despite these results, the question of mortality remains unanswered. The US Carvedilol and Australia-New Zealand databases are not sufficient to definitively state that beta-blockade reduces mortality. These databases also do not allow a sufficiently long follow-up (ie, > 12 months) in NYHA class III and IV patients to understand the long-term effects in these patients. For that reason, several ongoing trials in the United States and Europe continue to randomize patients. The Beta-Blocker Evaluation of Survival Trial (BEST)[100] and COPERNICUS trial will randomize patients to the nonselective, third-generation agents bucindolol and carvedilol. The CIBIS II[101] and MERIT-HF trials have randomized patients to the beta-1 selective agents bisoprolol and metoprolol. The CIBIS-2 trial has been terminated early for a presumed mortality benefit, although the data have yet to be revealed.

Although third-generation nonselective agents such as bucindolol, carvedilol, and labetalol have more antiadrenergic properties than beta-1 selective agents such as metoprolol, it is unclear if they protect the heart from sudden death better. One head-to-head trial of carvedilol and metoprolol, the COMET trial, will help to answer this important question.

HOW TO USE BETA-BLOCKERS

Beta-blockers can be difficult to titrate in patients with heart failure, and this therapy should be administered only by persons trained and familiar with it. Moreover, I recommend the following cautions when starting therapy.[96]

Beta-blockers are not rescue therapy. Patients in an unstable condition should not be started on beta-blockers. In general, candidates should be stable outpatients with class II, III, or perhaps early class IV heart failure (although data on class IV usage are currently lacking). When the large mortality studies are completed, we hope we will have insight into when and whom to treat with these promising agents.

Start low, go slow. Initial doses must be extremely low, such as one 3.125-mg carvedilol tablet twice a day—or half a tablet

if the patient is in class IV or has severe right-sided heart failure with jugular venous distention, ascites, and edema.

Thereafter, the patient should come back every week or 2 weeks, and the dose can be doubled at each visit, as tolerated, up to a target of 25 mg of carvedilol twice a day (if the patient weighs less than 85 kg) or 50 mg twice a day (if the patient weighs 85 kg or more). Titration may take months, especially in very ill patients. Patients should be told they should not expect to see any improvement for at least a month after the beta-blocker is started.

Watch for decompensation. Patients should weigh themselves every day and contact the physician immediately if they gain more than 2 or 3 pounds. Usually, such fluid retention responds to increasing the dosage of the diuretic or ACE inhibitor temporarily, but if it does not or if the patient seems about to go into cardiogenic shock, the beta-blocker should be reduced or stopped.

At each visit during titration, I also check the blood urea nitrogen level, because some patients with heart failure develop prerenal azotemia while taking beta-blockers.

REFERENCES

1. **Packer M.** How should physicians view heart failure?—The philosophical and physiological evolution of three conceptual models of the disease. Am J Cardiol 1993; 71:C3–C11.
2. **Massie BM, Berk MR, Brozena SC, et al for the FACET Investigators.** Can further benefit be achieved by adding flosequinan to patients with congestive heart failure who remain symptomatic on diuretic, digoxin, and an angiotensin converting enzyme inhibitor? Circulation 1993; 88:492–501.
3. **Packer M, Narahara KA, Elkayam U, et al and the Principal Investigators of the REFLECT Study.** Double-blind, placebo-controlled study of the efficacy of flosequinan in patients with chronic heart failure. J Am Coll Cardiol 1993; 22:65–72.
4. **The German and Austrian Xamoterol Group.** Double-blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. Lancet 1988; 1:489–493.
5. **Dibianco R, Shabetai R, Kostuk W, Moran J, Schlant RC, Wright R.** A comparison of oral milrinone, digoxin, and their combination in the treatment of patients with chronic heart failure. N Engl J Med 1989; 320:677–683.
6. **Uretsky BF, Generalovick T, Reddy PS, Spangenberg RB, Follansbee WP.** The acute hemodynamic effects of a new agent, MDL 17,043, in the treatment of congestive heart failure. Circulation 1983; 67:823–828.
7. **Monrad ES, Baim DS, Smith HS, Lanoue AS.** Milrinone, dobutamine, and nitroprusside: comparative effects on hemodynamics and myocardial energetics in patients with severe congestive heart failure. Circulation 1986; 73(Suppl III):III-168–III-174.
8. **Gottlieb SS, Kukin ML, Penn J, et al.** Sustained hemodynamic response to flosequinan in patients with heart failure receiving angiotensin-converting enzyme inhibitors. J Am Coll Cardiol 1993; 22:963–967.
9. **Packer M, Carver JR, Chesebro JH, et al and the PROMISE investigators.** Effect of milrinone on mortality in severe chronic heart failure. The prospective randomized milrinone survival evaluation (PROMISE). N Engl J Med 1991; 325:1468–1475.
10. **Packer M, Rouleau J, Swedberg K, Pitt B, Fisher L, Klepper M, and the PROFILE Investigators & Coordinators.** Effect of flosequinan on survival in chronic heart failure: Preliminary results of the PROFILE study (abstract). Circulation 1993; 88(Suppl I):I-301.
11. **Califf RM, Adams KF, McKenna WJ, et al.** A randomized controlled trial of epoprostenol therapy for severe congestive heart failure: The Flolan International Randomized Survival Trial (FIRST). Am Heart J 1997; 134:44–54.
12. **The Xamoterol in Severe Heart Failure Study Group.** Xamoterol in severe heart failure. Lancet 1990; 336:1–6.
13. **Dies F, Krell MJ, Whitlow P, et al.** Intermittent dobutamine in ambulatory outpatients with chronic cardiac failure (abstract). Circulation 1986; 74(Suppl II):II-38.
14. **Eichhorn EJ, Bristow MR.** Medical therapy can improve the biologic properties of the chronically failing heart: A new era in the treatment of heart failure. Circulation 1996; 94:2285–2296.
15. **Pfeffer JM, Pfeffer MA, Braunwald E.** Influence of chronic captopril therapy on the infarcted left ventricle of the rat. Circ Res 1985; 57:84–95.
16. **Spinale FG, Holzgrefe HH, Mukherjee R, et al.** Angiotensin-converting enzyme inhibition and the progression of congestive cardiomyopathy. Effects on left ventricular and myocyte structure and function. Circulation 1995; 92:562–578.
17. **Sabbah HN, Shimoyama H, Kono T, et al.** 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.
18. **McDonald KM, Rector T, Carlyle PF, Francis GS, Cohn JN.** Angiotensin-converting enzyme inhibition and beta-adrenoceptor blockade regress established ventricular remodeling in a canine model of discrete myocardial damage. J Am Coll Cardiol 1994; 24:1762–1768.
19. **Sharpe N, Smith H, Murphy J, Greaves S, Hart H, Gamble G.** Early prevention of left ventricular dysfunction after myocardial infarction with angiotensin-converting-enzyme inhibition. Lancet 1991; 337:872–876.
20. **Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E.** Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med 1988; 319:80–86.
21. **Konstam MA, Rousseau MF, Kronenberg MW, et al for the SOLVD Investigators.** Effects of the angiotensin converting enzyme inhibitor enalapril on the long-term progression of left ventricular dysfunction in patients with heart failure. Circulation 1992; 86:431–438.
22. **Greenberg B, Quinones MA, Koilpillai C, et al 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.
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 (CONSENSUS). N Engl J Med 1987; 316:1429–1435.
24. **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.
25. **Pfeffer M, Braunwald E, Moye L, et al on behalf of the SAVE investigators.** Effect of captopril on mortality and morbidity in patients with left ventricular, dysfunction after myocardial infarction. Results of survival and ventricular enlargement trial. N Engl J Med 1992;327:669–677.
26. **Sadoshima J, Xu Y, Slayter HS, Izumo S.** Autocrine release of angiotensin II mediates stretch-induced hypertrophy of cardiac myocytes in vitro. Cell 1993; 75:977–984.
27. **Edwards BS, Zimmerran RS, Schwab TR, Heublein DM, Burnett JC.** Atrial stretch, not pressure, is the principal determinant controlling

the acute release of atrial natriuretic factor. Circ Res 1988; 62:191–195.
28. **Leimbach WN, Wallin BG, Victor RG, Aylward PE, Sundlof G, Mark AL.** Direct evidence from intraneural recordings for increased central sympathetic outflow in patients with heart failure. Circulation 1986; 73:913–919.
29. **Bristow, MR, Abraham WT.** Anti-adrenergic effects of angiotensin converting enzyme inhibitors. Eur Heart J 1995;16:37–41.
30. **Malik KU, Nasjletti A.** Facilitation of adrenergic transmission by locally generated angiotensin II in rat mesenteric arteries. Circ Res 1976; 38:26–30.
31. **McLeod AA, Brown JE, Kuhn C, et al.** Differentiation of hemodynamic, humoral and metabolic responses to β1- and β2-adrenergic stimulation in man using atenolol and propranolol. Circulation 1983; 67:1076–1084.
32. **Levine B, Kalman J, Mayer L, Fillit HM, Packer M.** Elevated circulating levels of tumor necrosis factor in severe chronic heart failure. N Engl J Med 1990; 323:236–241.
33. **Torre-Amione G, Kapadia SR, Lee J, et al.** Tumor necrosis factor-α and tumor necrosis factor receptors in the failing human heart. Circulation 1996; 93:704–711.
34. **Cody RJ, Haas GJ, Binkley PF, Capers Q, Kelley R.** Plasma endothelin correlates with the extent of pulmonary hypertension in patients with chronic congestive heart failure. Circulation 1992; 85:504–509.
35. **Cohn JN.** Is there a role for endothelin in the natural history of heart failure? Circulation 1996; 94:604–606.
36. **Kiowski W, Sutsch G, Hunziker P, et al.** Evidence for endothelin-1 mediated vasoconstriction in severe chronic heart failure. Lancet 1995; 346:732–736.
37. **Gibbons GH, Pratt RE, Dzau VJ.** Vascular smooth muscle cell hypertrophy vs hyperplasia. Autocrine transforming growth factor-β1 expression determines growth response to angiotensin II. J Clin Invest 1992; 90:456–461.
38. **Schneider MD, Parker TG.** Cardiac myocytes as targets for the action of peptide growth factors. Circulation 1990; 81:1443–1456.
39. **Parker TG, Packer SE, Schneider MD.** Peptide growth factors can provoke "fetal" contractile protein gene expression in rat cardiac myocytes. J Clin Invest 1990; 85:507–514.
40. **Francis GS.** The relationship of the sympathetic nervous system and the renin-angiotensin-aldosterone system in congestive heart failure. Am Heart J 1989; 118:642–648.
41. **Packer M, Lee WH, Kessler PD, Gottlieb SS, Bernstein JL, Kukin ML.** Role of neurohormonal mechanisms in determining survival in patients with severe chronic heart failure. Circulation 1987; 75(Suppl IV):IV-80–IV-92.
42. **Katz A.** The cardiomyopathy of overload: an unnatural growth response in the hypertrophied heart. Ann Intern Med 1994; 121:363–371.
43. **Nadal-Ginard B.** Commitment, fusion, and biochemical differentiation of a myogenic cell line in the absence of DNA synthesis. Cell 1978; 15:855–864.
44. **Gerdes AM, Kellerman SE, Moore JA, et al.** Structural remodeling of cardiac myocytes in patients with ischemic cardiomyopathy. Circulation 1992; 86:426–430.
45. **Anversa P, Capasso JM.** Cardiac hypertrophy and ventricular remodeling. Lab Invest 1991; 64:441–445.
46. **Sabbah HN, Goldstein S.** Ventricular remodeling: consequences and therapy. Eur Heart J 1993; 14(Suppl C):24–29.
47. **Cohn, JN.** Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition. Circulation 1995; 91:2504–2507.
48. **Grossman W, Jones D, McLaurin LP.** Wall stress and patterns of hypertrophy in the human left ventricle. J Clin Invest 1975; 56:56–64.
49. **Hasenfuss G, Holubarsch C, Heiss HW, et al.** Myocardial energetics in patients with dilated cardiomyopathy. Influence of nitroprusside and enoximone. Circulation 1989; 80:51–64.
50. **Nelson RR, Gobel FL, Jorgensen CR, Wang K, Wang Y, Taylor HL.** Hemodynamic predictors of myocardial oxygen consumption during static and dynamic exercise. Circulation 1974; 50:1179–1189.
51. **Katz AM.** Cellular mechanisms in congestive heart failure. Am J Cardiol 1988; 62:3A–8A.
52. **Eichhorn EJ, Heesch CM, Barnett JH, et al.** Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol 1994; 24:1310–1320.
53. **Lowes BD, Minobe W, Abraham WT, et al.** Changes in gene expression in the intact human heart. Downregulation of α-myosin heavy chain in hypertrophied, failing ventricular myocardium. J Clin Invest 1997; 100:2315–2324.
54. **Yokoyama T, Nakano M, Bednarczyk JL, McIntyre BW, Entman M, Mann DL.** Tumor necrosis factor-α provokes a hypertrophic growth response in adult cardiac myocytes. Circulation 1997; 95:1247–1252.
55. **Schwartz K, Carrier, L, Mercadier, J-J, Lompre, A-M, Boheler, KR.** Molecular phenotype of the hypertrophied and failing myocardium. Circulation 1993; 87(Suppl VII):VII-5–VII-10.
56. **Arai M, Alpert NR, MacLennan DH, Barton P, Periasamy M.** Alterations in sarcoplasmic reticulum gene expression in human heart failure. Circ Res 1993; 72:463–469.
57. **Cory CR, McCutcheon LJ, O'Grady M, Pang AW, Geiger JD, O'Brien J.** Compensatory downregulation of myocardial Ca channel in SR from dogs with heart failure. Am J Physiol 1993; 264:H926–H937.
58. **Weiss MB, Ellis K, Sciacca RR, Johnson LL, Schmidt DH, Cannon PJ.** Myocardial blood flow in congestive and hypertrophic cardiomyopathy. Relationship to peak wall stress and mean velocity of circumferential fiber shortening. Circulation 1976; 54:484–494.
59. **Weber KT, Anversa P, Armstrong PW, et al.** Remodeling and reparation of the cardiovascular system. J Am Coll Cardiol 1992; 20:3–16.
60. **Weber KT, Brilla CG.** Pathological hypertrophy and cardiac interstitium. Fibrosis and renin-angiotensin-aldosterone system. Circulation 1991; 83:1849–65.
61. **Sabbah HN, Sharov VG, Cook JM, Shimoyama H, Lesch M.** Accumulation of collagen in the cardiac interstitium of dogs with chronic heart failure is associated with decreased capillary density and increased oxygen diffusion distance (abstract). J Am Coll Cardiol 1995; 25:222A.
62. **Shimoyama H, Sabbah HN, Sharov VG, Cook J, Lesch M, Goldstein S.** Accumulation of interstitial collagen in the failing left ventricular myocardium is associated with increased anaerobic metabolism among affected cardiomyocytes (abstract). J Am Coll Cardiol 1994; 23:98A.
63. **Parodi O, DeMaria R, Oltrona L, et al.** Myocardial blood flow distribution in patients with ischemic heart disease or dilated cardiomyopathy undergoing heart transplantation. Circulation 1993; 88:509–522.
64. **Mann DL, Kent RL, Parsons B, Cooper G 4th.** Adrenergic effects on the biology of the adult mammalian cardiocyte. Circulation 1992; 85:790–804.
65. **Tan LB, Jalil JE, Pick R, Janicki JS, Weber KT.** Cardiac myocyte necrosis induced by angiotensin II. Circ Res 1991; 69:1185–1195.
66. **Thompson CB.** Apoptosis in the pathogenesis and treatment of disease. Science 1995; 267:1456–1462.
67. **Packer M, Francis GS, Abrams J, et al.** Oral milrinone increases the risk of sudden death in severe chronic heart failure: The PROMISE trial (abstract). Circulation 1991; 84(Suppl II):II-310.
68. **Kessler P, Packer M, Medina N, Yushak M.** Long-term hemodynamic and clinical responses to flosequinan, a new once-daily balanced direct-acting vasodilator, in severe heart failure (abstract). Circulation 1986; 74(Suppl II):II-509.
69. **Yui Y, Nakajima H, Kawai C, Murakami T.** Prostacyclin therapy in patients with congestive heart failure. Am J Cardiol 1982; 50:320–324.
70. **Hall SA, Cigarroa CG, Marcoux L, Risser RC, Grayburn PA, Eichhorn EJ.** Time course of improvement in left ventricular function, mass, and geometry in patients with congestive heart failure treated with β-adrenergic blockade. J Am Coll Cardiol 1995; 25:1154–1161.
71. **Francis GS, Cohn JN, Johnson G, Rector TS, Goldman S, Simon A, for the V-HeFT VA Cooperative Studies Group.** Plasma norepinephrine, plasma renin activity, and congestive heart failure. Circulation 1993; 87(Suppl VI):VI-40–VI-48.
72. **Engelmeier RS, O'Connell JB, Walsh R, et al.** Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. Circulation 1985; 72:536–546.
73. **Ikram H, Fitzpatrick D.** Double blind trial of chronic oral beta blockade in congestive cardiomyopathy. Lancet 1981; 2:490–493.

74. **Currie PJ, Kelly KJ, McKenzie, et al.** Oral beta-adrenergic blockade with metoprolol in chronic severe dilated cardiomyopathy. J Am Coll Cardiol 1984; 3:203–209.
75. **Gilbert EM, Anderson JL, Deitchman D, et al.** Chronic β-blocker-vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: A double-blind, randomized study of bucindolol versus placebo. Am J Med 1990; 88:223–229.
76. **Pollock SG, Lytash J, Tedesco C, et al.** Usefulness of bucindolol in congestive heart failure. Am J Cardiol 1990; 66:603–607.
77. **Woodley SL, Gilbert EM, Anderson JL, et al.** β-blockade with bucindolol in heart failure due to ischemic vs idiopathic dilated cardiomyopathy. Circulation 1991; 84:2426–2441.
78. **Metra M, Nardi M, Giubbini R, DeiCas L.** Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol 1994; 24:1678–1687.
79. **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.
80. **Waagstein F, Bristow MR, Swedberg K, et al for the Metoprolol in Dilated Cardiomyopathy (MDC) Trial Study Group.** Beneficial effects of metoprolol in idiopathic dilated cardiomyopathy. Lancet 1993; 342:1441–1446.
81. **Bristow MR, O'Connell JB, Gilbert EM, et al for the Bucindolol Investigators.** Dose-response of chronic β-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Circulation 1994; 89:1632–1642.
82. **Wisenbaugh T, Katz I, Davis J, et al.** Long-term (3 month) effects of a new beta-blocker (nebivolol) on cardiac performance in dilated cardiomyopathy. J Am Coll Cardiol 1993; 21:1094–1100.
83. **Paolisso G, Gambardella A, Marrazzo G, et al.** Metabolic and cardiovascular benefits deriving from β-adrenergic blockade in chronic congestive heart failure. Am Heart J 1992; 123:103–110.
84. **Krum H, Sackner-Bernstein J, Goldsmith RL, et al.** Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. Circulation 1995; 92:1499–1506.
85. **Fisher ML, Gottlieb SS, Plotnick GD, et al.** Beneficial effects of metoprolol in heart failure associated with coronary artery disease: A randomized trial. J Am Coll Cardiol 1994; 23:943–950.
86. **Australia-New Zealand Heart Failure Research Collaborative Group.** Effects of carvedilol, a vasodilator-β-blocker, in patients with congestive heart failure due to ischemic heart disease. Circulation 1995; 92:212–218.
87. **Packer M, Colucci WS, Sackner-Bernstein JD, et al for the PRECISE Study Group.** Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE trial. Circulation 1996; 94:2793–2799.
88. **Bristow MR, Gilbert EM, Abraham WT, et al for the MOCHA Investigators.** Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. Circulation 1996; 94:2807–2816.
89. **CIBIS Investigators and Committees.** A randomized trial of beta-blockade in heart failure: The Cardiac Insufficiency Bisoprolol Study (CIBIS). Circulation 1994; 90:1765–1773.
90. **Eichhorn EJ.** Do β-blockers have a role in patients with congestive heart failure? Cardiol Clin 1994; 12:133–142.
91. **Doughty RN, MacMahon S, Sharpe N.** Beta-blockers in heart failure: Promising or proved? J Am Coll Cardiol 1994; 23:814–821.
92. **Eichhorn EJ, Bedotto JB, Malloy CR, et al.** Effect of beta-adrenergic blockade on myocardial function and energetics in congestive heart failure: improvements in hemodynamic, contractile, and diastolic performance with bucindolol. Circulation 1990; 82:473–483.
93. **Tsutsui H, Spinale FG, Nagatsu M, et al.** Effects of chronic β-adrenergic blockade on the left ventricular and cardiocyte abnormalities of chronic canine mitral regurgitation. J Clin Invest 1994; 93:2639–2648.
94. **Bristow MR, Gilbert EM, Lowes BD, et al.** Changes in myocardial gene expression associated with β-blocker-related improvement in ventricular systolic function (abstract). Circulation 1997; 96(Suppl I):I-92.
95. **Lowes BD, Gill EA, Rodriguez-Larrain J, Abraham WT, Bristow MR.** Carvedilol is associated with a reversal of remodeling in chronic heart failure (abstract). Circulation 1996; 94(Suppl I):I-407.
96. **Eichhorn EJ, Bristow MR.** Practical guidelines for initiation of β-adrenergic blockade in patients with chronic heart failure. Am J Cardiol 1997; 79:794–798.
97. **Packer M, Bristow MR, Cohn JN, et al for the U.S. Carvedilol Heart Failure Study Group.** Effect of carvedilol on morbidity and mortality in chronic heart failure. N Engl J Med 1996; 334:1349–1355.
98. **Colucci WS, Packer M, Bristow MR, et al for the US Carvedilol Heart Failure Study Group.** Carvedilol inhibits clinical progression in patients with mild symptoms of heart failure. Circulation 1996; 94:2800–2806.
99. **Australia/New Zealand Heart Failure Research Collaborative Group.** Randomised, placebo-controlled trial of carvedilol in patients with congestive heart failure due to ischaemic heart disease. Lancet 1997; 349:375–380.
100. **The BEST Steering Committee.** Design of the Beta-Blocker Evaluation Survival Trial (BEST). Am J Cardiol 1995; 75:1220–1223.
101. **The CIBIS II Scientific Committee.** Design of the cardiac insufficiency bisoprolol study II (CIBIS II). Fundam Clin Pharmacol 1997; 11:138–142.

ADDRESS: *Eric J. Eichhorn, MD, Cardiac Catheterization Laboratory (IIIA2), University of Texas Southwestern and Dallas Veterans Administration Medical Centers, 4500 S. Lancaster, Dallas, TX 75216; e-mail: eichhorn@ryburn.swmed.edu.*