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Editorial Comment

Phosphodiesterase Inhibitors in Refractory Heart Failure: Bridge to Beta-Blockade?*

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In the clinical management of heart failure, two truths have become evident: Excess is harmful; and patience is a virtue. The first truth relates to the stimulation of the sympathetic and renin–angiotensin systems in response to the acute hemodynamic derangements of heart failure. These systems promote sodium and water retention, vasoconstriction and contractility in an effort to enhance cardiac performance through physiologic mechanisms (1). However, continued neurohormonal activation elicits harmful pathophysiologic consequences, such as attenuation of cardiopulmonary baroreflex inhibition, downregulation of $beta_1$-adrenoreceptor density, uncoupling of beta-adrenoreceptors from the G-protein–adenylcyclase complex, myocyte loss, systemic vasoconstriction and, ultimately, ventricular remodeling and increased wall stress (1–3). Thus, neurohormonal activation leads to the inevitable progression of heart failure after resolution of the initial cardiopathic insult—the so-called neurohormonal hypothesis (1). Presuming this hypothesis to be valid, treatments that promote the physiologic aberrations of neurohormonal activation should produce hemodynamic benefits in the short term but accelerate heart failure progression in the long term. Such is the case with the prolonged use of nonglycoside inotropic agents such as the phosphodiesterase inhibitors (4–7). Alternatively, disruption of neurohormonal activation should slow heart failure progression, as is the case with the angiotensin-converting enzyme (ACE) inhibitors (8–10).

The second truth (a Stoic principle) relates to the actual application of medications for heart failure. Some drugs, such as ACE inhibitors, should not be immediately applied at full doses in patients with symptomatic heart failure because these drugs may not be tolerated. Hypotension often limits the initial dosing of ACE inhibitors. As a result, ACE inhibitors should be started at lower doses and gradually titrated upward. A successful titration of ACE inhibitors to therapeutic doses results in a delay in heart failure progression and improved survival. Patience proves prudent. Similar principles apply to beta-adrenergic blocking agents. Impaired inotropy and increased systemic vascular resistance result in exacerbations of heart failure when beta-adrenergic blockers are administered over too short a period or at too high a dose in patients with chronic heart failure (2,11). Doses must be started low and patiently increased to overcome short-term intolerance. Even so, in patients with mild to moderate symptomatic heart failure, the initial titration of beta-adrenergic blockers will fail in 4% to 8% (12–17). For those patients who tolerate beta-adrenergic blockers, delayed heart failure progression, improved cardiac performance and improved survival have been demonstrated in several studies (12–16).

The use of beta-adrenergic blockers in patients with New York Heart Association functional class IV or refractory heart failure has not been adequately studied. Clinical experience tells us that a substantially greater proportion of patients will be intolerant of beta-adrenergic blockers (10,11,18). Because ACE inhibitors are beneficial in patients in functional class IV (8), one would also expect beta-adrenergic blockers to be of benefit if only they could be successfully applied. In such patients, the initial administration of beta-adrenergic blockers may be difficult, but quiet determination will most likely prove fruitful in the long run. In an unassuming and nondramatic manner, beta-adrenergic blockers will dampen the sympathetic nervous system, slow the heart rate and improve left ventricular ejection fraction and may prolong survival. In this manner, the principles of stoicism (patience and endurance) may be the key to success of beta-adrenergic blocker therapy in severe heart failure.

However, there will still be a certain fraction of patients with severe or refractory heart failure unable to tolerate beta-adrenergic blockers at any doses or over any titration period, regardless of their or their physician's determination. How, then, to overcome short-term intolerance? Why not change philosophies and take an Epicurean approach? Phosphodiesterase inhibitors (the inodilators) provide rapid and dramatic improvements in cardiac performance, even in patients with severe heart failure, producing rapid relief of heart failure symptoms. But, in true Epicurean fashion, prolonged use of inotropic agents shortens survival, at least in part by promoting myocyte loss as well as arrhythmogenesis and sudden death (4–7,19,20). In contrast, beta-adrenergic blockers protect against myocyte loss, are antiarrhythmogenic and may potentially prevent sudden death (2,21). When used together, phosphodiesterase inhibitors may conceivably overcome the initial hemodynamic intolerance of beta-adrenergic blockers in patients with severe heart failure. Beta-adrenergic blockers will quiet the sympathetic nervous system, and the culmination of this combination would be the expression of the advantages of both and the cancellation of their negative qualities. The conjoining of Stoic and Epicurean philosophies may prove symbiotic in the management of refractory heart failure.

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So now we are faced with two common and practical issues: how to wean the patient with refractory heart failure from intravenous inotropic agents and then how to apply beta-adrenergic blockers to reduce future episodes of cardiac decompensation? Shakar et al. (22), in this issue of the Journal, chose to use the oral phosphodiesterase inhibitor enoximone to tackle both problems simultaneously. They intended to wean patients from intravenous inotropic agents by using oral enoximone (23), continue the enoximone for a period of time to attain hemodynamic stabilization, initiate and titrate metoprolol (a $beta_1$-selective adrenoceptor blocker) and then wean the patients from enoximone while continuing metoprolol. Enoximone was an obvious choice for this task because it was available in oral formulation. This drug and drugs of its class promote contractility by preventing the intracellular degradation of cyclic adenosine monophosphate, a mechanism independent of beta-adrenergic receptor signaling (2,6,24). Thus, metoprolol would not prevent the desired inotropic effects of enoximone. Preliminary data have suggested that the combination of phosphodiesterase inhibitors and beta-adrenergic receptor blockers in heart failure is tolerated and that hemodynamic changes are beneficial (25,26). Although the main presumption is that the enhanced contractility imparted by phosphodiesterase inhibitors is the mechanism that supports the initiation of beta-adrenergic blockade, patients with refractory heart failure taking intravenous adrenergic agonists, when stabilized, also seem to tolerate beta-blocker initiation (27). Because beta-adrenergic blockers attenuate the inotropic effects of beta-adrenergic agonists, peripheral effects of inotropic/inodilator agents may be important in allowing the administration of beta-adrenergic blockers.

Shakar et al. (22) specifically targeted patients with functional class IV heart failure. Thirty patients were studied, 18 of whom met the definition of refractory heart failure (28) and were receiving intravenous inotropic agents, 9 of whom had symptoms too unstable to attempt beta-adrenergic blockade, and 3 of whom were known to be previously intolerant of beta-adrenergic blockers. It is doubtful any of these patients could tolerate beta-adrenergic blockade. Symptoms were successfully stabilized with enoximone in all patients (although enoximone was discontinued in one patient 5 months later because of syncope), and all 18 patients receiving intravenous inotropic agents were successfully weaned from their drugs with oral enoximone. Twenty-eight of 30 patients were ultimately challenged with metoprolol, and 23 (82%) tolerated the drug. These patients continued metoprolol therapy until death or heart transplantation, a mean of 21 months (lead follow-up, nearly 7 years). Only one-half of patients could be weaned from enoximone while continuing metoprolol, lending credence to the hemodynamic supportive role that enoximone was providing. Metoprolol (with or without enoximone) produced a sustained improvement in left ventricular ejection fraction, in functional class and in the reduction of the number of hospital admissions over the course of metoprolol administration, suggesting a real impact on the progression of heart failure in these severely ill patients. One of the major observations of this study was that survival appeared to be improved in patients in functional class IV by the addition of metoprolol to triple therapy. Only 5 patients (17%) died of cardiac causes, and one-half never required heart transplantation (22). The 1-year survival rate (censored at the time of heart transplantation) for patients taking metoprolol was 81% (95% confidence interval 64% to 98%), substantially better than the 1-year survival of patients in functional class IV in the experimental arm of the CONSENSUS I trial (54%) or the control arm of the PROMISE trial (61%) (5,8). This comparatively better survival with metoprolol is presumptive evidence that beta-adrenergic blockade is beneficial to patients with functional class IV heart failure receiving triple therapy and that enoximone makes this a tolerated treatment approach. In other words, enoximone served as a bridge to beta-blocker therapy.

Surprisingly, because one-half of patients could not be weaned from enoximone, Shakar et al. (22) have unwittingly broached the subject of combining Epicurean and Stoic principles over the long term. The apparent improved survival in the study suggests, as hypothesized, that the combination of phosphodiesterase inhibitors with beta-adrenergic blockers may produce all the benefits of both without the liabilities of either. "Quintuple therapy" may therefore be a legitimate consideration in patients with severe heart failure.

But let us not get ahead of ourselves. This optimism evolves from a study with several problems: 1) The study involved only 30 patients compared with 253 patients in functional class IV in the CONSENSUS I trial and 457 such patients in the PROMISE trial (5,8). Despite this huge difference in subject numbers, a p value of 0.01 was calculated comparing the 1-year survival rate of metoprolol-treated patients with that of patients in the CONSENSUS I and PROMISE trials who received triple therapy only (22). Still, we must keep in mind that only several more deaths in the study might have raised considerable doubt as to whether metoprolol confers a survival advantage in these patients. 2) The study was retrospective and as such the influence of hidden biases cannot be excluded. For instance, 30 patients were studied, but they are not described as "consecutive," which implies that some discrimination was utilized in their inclusion that could influence the tolerability and outcome of beta-adrenergic blocker therapy in either a favorable or negative direction. More problematic, was enoximone unsuccessful in weaning some patients from intravenous inotropic therapy, so that they never underwent metoprolol challenge and were thus not included in this study? Could some of these patients have somehow tolerated metoprolol and have accrued long-term benefit? This scenario is not likely, but their "intention to treat" inclusion could have provided a more meaningful perspective of the proposed enoximone/metoprolol treatment approach to refractory heart failure. 3) We do not actually have a historical denominator that delineates the proportion of patients in functional class IV intolerant of metoprolol. We can therefore only infer that the use of enoximone represents an advance. 4) A true control group was obviously lacking in this study. 5) The findings of this study using metoprolol may not be generalizable to the third-generation beta-adrenergic block-

ers, such as carvedilol or bucindolol. 6) No prospective neurohormonal data were generated to demonstrate the proposed dampening of the sympathetic nervous system in these patients, one-half of whom continued receiving enoximone. The demonstration of sustained, diminished neurohormonal levels in those patients receiving metoprolol (±enoximone) would have been compelling supportive evidence of the favorable effects of beta-adrenergic blockade on the natural history of severe heart failure, albeit that a demonstration of attenuated neurohormonal status has not been uniformly shown in beta-blocker trials (29–31).

Where does the information from this small pilot study lead us? We need to determine with certainty whether beta-adrenergic blockade produces a survival advantage in patients with severe or refractory heart failure over triple-therapy alone. This determination will require prospective, randomized trials. The study by Shakar et al. (22) provides us with a means to eliminate the problem of beta-adrenergic blocker intolerance, which would confound such prospective, randomized trials. The use of up-front enoximone would avoid the bias introduced by drug intolerability during run-in test periods that determine a subject's eligibility for randomization and have plagued previous beta-adrenergic blocker trials (12–18). The study also hints at a solution to the problem facing many outpatients with end-stage heart failure who are receiving intravenous inodilator therapy: the Epicurean trade-off of improved heart failure symptoms in the short run but shortened survival in the long run. The study by Shakar et al. (22) suggests that a sizable fraction of these outpatients should tolerate the initiation and titration of beta-adrenergic blockers. Many of these patients will be weanable from the intravenous inodilators—hopefully, to enjoy the potential benefits of heart failure symptom palliation without the expectation of shortened survival.

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References

1. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992;20:248–54.
2. Bristow MR. Pathophysiologic and pharmacologic rationales for clinical management of chronic heart failure with beta-blocking agents. Am J Cardiol 1993;71:12C–22C.
3. Rosenbaum JS, Ginsburg R, Billingham ME, Hoffman BB. Effects of adrenergic antagonists on cardiac morphologic and functional alterations in rats harboring pheochromocytoma. J Pharmacol Exp Ther 1987;241:354–60.
4. Uretsky BF, Jessup M, Konstam MA, et al. Multicenter trial of oral enoximone in patients with moderate to moderately severe congestive heart failure: lack of benefit compared with placebo. Circulation 1990;82:774–80.
5. Packer M, Carver JR, Rodeheffer RJ, et al., for the Promise Study Research Group. Effect of oral milrinone on mortality in severe chronic heart failure. N Engl J Med 1991;325:1468–75.
6. Vernon MW, Heel RC, Brogden RN. Enoximone: a review of its pharmacological properties and therapeutic potential. Drugs 1991;42:997–1017.
7. Narahara KA, and the Western Enoximone Study Group. Oral enoximone therapy and chronic heart failure: a placebo-controlled randomized trial. Am Heart J 1991;121:1471–9.
8. 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;316:1429–35.
9. Cohn JN, Johnson G, Ziesche S, et al. A comparison of enalapril with hydralazine-isosorbide dinitrate in the treatment of chronic congestive heart failure. N Engl J Med 1991;325:303–10.
10. Chatterjee K. Heart failure therapy in evolution. Circulation 1996;94:2689–93.
11. Haber HL, Gimple LW, Simek CL, et al. Why do patients with congestive heart failure tolerate the induction of beta-blocker therapy? [abstract]. Circulation 1992;86 Suppl I:I-17.
12. 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;94:2793–9.
13. 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;94:2800–6.
14. 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;94:2807–16.
15. Packer M, Bristow MR, Cohn JN, et al., for the US Carvedilol Heart Failure Study Group. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. N Engl J Med 1996;334:1349–55.
16. Australia/New Zealand Heart Failure Research Collaborative Group. Randomized, placebo-controlled trial of carvedilol in patients with heart failure due to ischaemic heart disease. Lancet 1997;349:375–80.
17. 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;342:1441–6.
18. Krum H, Sackner-Bernstein JD, 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;92:1499–506.
19. Dies F. Intermittent dobutamine in ambulatory patients with chronic cardiac failure. Br J Clin Pract 1986;45 Suppl:37–40.
20. The Xamoterol in Severe Heart Failure Study Group. Xamoterol in severe heart failure. Lancet 1990;336:1–6.
21. Kendall MJ, Lynch KP, Hjalmarson A, Kjekhus J. Beta-blockers and sudden cardiac death. Ann Intern Med 1995;123:358–67.
22. Shakar SF, Abraham WT, Gilbert EM, et al. Combined oral positive inotropic and beta-blocker therapy for treatment of refractory class IV heart failure. J Am Coll Cardiol 1998;31:1336–40.
23. Lee HR, Hershberger RE, Port JD, et al. Low-dose enoximone in subjects awaiting cardiac transplantation: clinical results and effects on beta-adrenergic receptors. J Thorac Cardiovasc Surg 1991;102:246–58.
24. Chatterjee K. Newer oral inotropic agents: phosphodiesterase inhibitors. Crit Care Med 1990;18:534–8.
25. Galie N, Branzi A, Magnani G, et al. Effect of enoximone alone and in combination with metoprolol on myocardial function and energetics in severe congestive heart failure: improvement in hemodynamic and metabolic profile. Cardiovasc Drugs Ther 1993;7:337–47.
26. Travill CM, Pugh S, Noble MI. The inotropic and hemodynamic effects of intravenous milrinone when reflex adrenergic stimulation is suppressed by beta-adrenergic blockade. Clin Ther 1994;16:783–92.
27. Patten RD, Fisher ML, Greenberg NL, Gottlieb SS. Beta-blocker therapy in inotropic supported congestive heart failure patients [abstract]. Circulation 1992;86 Suppl I:I-645.
28. De Marco T, Chatterjee K. Refractory heart failure: a therapeutic approach. J Intensive Care Med 1996;11:121–48.
29. Olsson G, Daleskog M, Hjerndahl R, Rehnqvist N. Unchanged peripheral sympathetic activity following withdrawal of chronic metoprolol treatment: a study of noradrenaline concentrations and kinetics in plasma. Br J Clin Pharmacol 1984;18:573–9.
30. Andersson B, Blomstrom-Lundqvist C, Hedner T, Waagstein F. Exercise hemodynamics and myocardial metabolism during long-term beta-adrenergic blockade in severe heart failure. J Am Coll Cardiol 1991;18:1059–66.
31. Gilbert EM, Anderson JL, Deitchman D, et al. Chronic beta-blocker-vasodilator therapy improves cardiac function in idiopathic dilated cardiomyopathy: a double blind, randomized study of bucindolol vs placebo. Am J Med 1990;88:223–9.