Journal of the American College of Cardiology
© 1999 by the American College of Cardiology
Published by Elsevier Science Inc.

Vol. 34, No. 7, 1999
ISSN 0735-1097/99/$20.00
PII S0735-1097(99)00476-3

EDITORIAL COMMENT

Angiotensin-Converting Enzyme Inhibitors and Cytokines in Heart Failure: Dose and Effect?*

James B. Young, MD
Cleveland, Ohio

Pharmacotherapeutic management of patients with heart failure has become extraordinarily complicated and requires several drugs in most patients (1). This is because our understanding of the pathophysiology of the syndrome has increased over the last two decades, and treatment schemes have evolved in direct response to observations made clinically and experimentally. Clinical trials completed over this period have defined better practices, and simply treating heart failure patients with digoxin and diuretic agents is now passe. Angiotensin-converting enzyme (ACE) inhibitors and beta-adrenergic blockers, often combined with digoxin and diuretic agents, have emerged as quintessential agents to decrease heat failure's troubling morbidity and mortality. Nonetheless, the reasons why these important treatment schemes work are not completely understood, and contention arises when proper dosing strategies are debated. Initially heart failure treatments and drug dosages were chosen based on favorable hemodynamic responses to vasodilators, in particular, those acutely produced in the coronary care unit or cardiac catheterization laboratory (2). In the late 1960s and early 1970s, there was some suggestion that drugs with vasodilating capabilities would result in better exercise tolerance and diminished symptoms (3). In 1980, the seminal Veterans Administration Cooperative Vasodilator in Heart Failure Study (now commonly referred to as V-HeFT-I) was initiated to test the concept that peripheral vasoconstriction contributed to progressive deterioration of left ventricular function and premature death in heart failure and that vasodilators would interdict this deleterious process (4). The results are well known and suggested that the combination of an aggressive dosing protocol of hydralazine (300 mg/day) combined with isosorbide dinitrate (160 mg/day), when added to digoxin and diuretic agents in patients with chronic congestive heart failure, had a favorable effect on left ventricular function and mortality. Sometimes overlooked is the fact that prazosin, an efficacious vasodilating and antihypertensive agent also studied in this project, fared no better than placebo with respect to outcomes. Indeed, not all vasodilating agents have done well in heart failure patients (note outcomes with respect to calcium channel blockers and prostacyclin, in particular) (1). Vasodilation, though likely important, seems not to be the major reason why patients with heart failure improved with some agents (despite the fact that many of these compounds have primarily been classified as such). The Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) published one year after V-HeFT-I in 1987, demonstrated that enalapril, then generally thought of as a vasodilating agent but known to have other putative beneficial properties, precipitated a dramatic mortality reduction when added to diuretic agents and digoxin in severely ill congestive heart failure patients (5). Subsequently the head-to-head comparison of enalapril with the hydralazine–isosorbide dinitrate combination showed the vasodilator with additional neurohumoral blocking and cyclooxygenase pathway effects (the ACE inhibitor) to be winner in the second V-HeFT trial (V-HeFT-II) (6). Studies of Left Ventricular Dysfunction (SOLVD) confirmed the importance of the ACE inhibitor, enalapril, in heart failure (7,8) and pointed out the importance of such an agent even when symptoms were minimal or entirely absent (8). These, as well as other now classic and often quoted clinical heart failure trials, established the overriding importance of ACE inhibitors in heart failure, but led Dr. J. N. Cohn to comment in 1996 (one decade after the publication of V-HeFT-I) that it was "... uncertain whether the remarkable response to these drugs [ACE inhibitors] in patients with cardiovascular disease can be attributed to hemodynamic effects, to the reduction in the level of angiotensin II in the plasma or tissue, to increased plasma concentrations of bradykinin or nitric oxide, or to inhibition of the sympathetic nervous system." (9). The debate about why ACE inhibitors are so effective in heart failure is highlighted by current efforts to employ angiotensin receptor blocking (ARB) agents to achieve the same benefits as ACE inhibitors, but without some of the ACE inhibitors' specific problems, which limit their use in ~20% of the target population (10). Absence of the ARB agents' ability to increase bradykinin likely makes these drugs easier to use and better tolerated, but may account for less pharmacologic benefit in some settings. As the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) trial design suggests, many investigators believe that ACE inhibitors combined with ARBs will benefit heart failure patients more than when either agent is used alone. However, might ACE inhibitor benefit in heart failure patients accrue through pharmacologic actions not previously characterized?

See page 2061

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

From the Kaufman Center for Heart Failure, Section of Heart Failure and Cardiac Transplant Medicine, The Cleveland Clinic Foundation, Cleveland, Ohio.

In this issue of *JACC*, Gullestad et al. (11) report data that strengthens already robust clinical trial information supporting the use of ACE inhibitors in heart failure, and thus documenting the fact that large doses of these compounds are necessary to most effectively ameliorate a perturbed humoral milieu, particularly the cytokine environment. Importantly, this study suggests that high doses of enalapril (40 mg daily) in patients with severe congestive heart failure significantly decreased interleukin (IL)-6 activity, which is believed to be important during detrimental heart failure remodeling (12–15). The decrease in IL-6 was associated with diminished interventricular septal thickness observed over time with echocardiography. These findings were not apparent when lower enalapril doses (5 mg daily) were used. Just as we have learned much in the last decade about which drugs to prescribe for patients with heart failure, the importance of proper dosing has also become more clear. We now know that some drugs are best prescribed at a fixed dose, whereas others should be force-titrated to target levels. Still, it was disappointing to see that not all seemingly evil inflammatory humors were interdicted by enalapril even at high doses, and it is likely that more direct immunomodulating treatments will be necessary to further improve the heart failure milieu when symptoms are severe. Also, it is not clear how ACE inhibitors produced the cytokine response noted. It is still uncertain whether there is a direct link between the reduction of IL-6 and inhibition of ACE. Still, this report supports the notion that higher rather than lower doses of ACE inhibitor are superior, and it is particularly intriguing because of the nagging question of just how ACE inhibitors work in heart failure.

Much information now suggests that cytokines, particularly tumor necrosis factor (TNF)-alpha and IL-6, play significant roles in various inflammatory conditions (16). It is not surprising, therefore, to see evidence supporting the contention that inflammatory cytokines are upregulated in patients with advanced heart failure (likely in an attempt to heal the injured myocardium given the fact that inflammation is the crux of our body's repair mechanism). Almost a decade ago, Levine et al. (17) demonstrated that circulating levels of TNF-alpha are elevated in patients with severe chronic heart failure, and subsequent studies noted that TNF-alpha increased in a variety of cardiac injury states including myocarditis (18) and acute coronary syndromes (19,20). All of these conditions have been shown to benefit from ACE inhibitors prescribed long term, and it is tantalizing to suggest, as have Gullestad et al. (11), that ACE inhibitor benefit relates to downregulation of cytokine activity, at least in part.

Of additional interest is the report from Gurantz et al. (21), that upregulation of the angiotensin type 1 receptor (AT1) on cardiac fibroblasts, which is important with respect to remodeling regulation, occurred after TNF-alpha exposure. Using quantitative competitive reverse transcription–polymerase chain reaction, these investigators found that norepinephrine, endothelin, atrial natriuretic peptide and bradykinin had no significant effect on AT1 messenger ribonucleic acid (mRNA) levels. In contrast, TNF-alpha produced a fivefold increase in AT1 mRNA, whereas angiotensin II, transforming growth factor-beta and basic fibroblast growth factor significantly reduced AT1 mRNA levels. These observations further link cytokine TNF-alpha to detrimental cardiac remodeling in heart failure.

Indeed, cytokines, and TNF-alpha, in particular, are an emerging therapeutic target in patients with heart failure. Important observations with respect to this issue include the fact that drugs that increase intracellular cyclic adenosine monophosphate (cAMP), such as pentoxifylline, amrinone and adenosine, prevent TNF-alpha mRNA accumulation by blocking the transcriptional activation of TNF-alpha (13). Thalidomide, in contrast, appears to diminish TNF-alpha by increasing mRNA degradation (22), whereas steroids (dexamethasone) appear to suppress TNF-alpha biosynthesis at the translational and transcriptional level (23). Whether any of these agents are effective in attenuating long-term heart failure morbidity and mortality is speculative, at best. Nonetheless, the recent report of Deseval et al. (24) is intriguing in that a soluble TNF-alpha receptor that neutralizes the biologic effect of circulating TNF-alpha improved functional status and quality of life in patients with advanced heart failure. This small but well-done study provides support for the concept of giving agents that attenuate cytokine perturbation in heart failure and sets the stage for a large randomized clinical trial of eternacept (14). It would be most interesting if ACE inhibitors, drugs already proven effective in heart failure, could be added to the list of agents that beneficially modulate cytokine production.

Several notes of caution must be raised about the Gullestad et al. study (11), some of which the authors themselves address. All patients were receiving low dose ACE inhibitor therapy at baseline blood sampling, and the effects of ACE inhibition de novo on these patients' cytokine levels are unknown. Furthermore, no placebo group was included, and we therefore cannot determine whether the changes, or lack thereof, in cytokine activity simply represent the natural variability of circulating levels of cytokines in heart failure. Indeed, Dibbs et al. (25) have recently examined variability in cytokine levels in patients with heart failure as compared with normal control subjects. Circulating levels of TNF-alpha, soluble TNF receptors 1 and 2, IL-6 and IL-6 receptor were measured daily, weekly and monthly in 10 patients with New York Heart Association (NYHA) functional class III congestive heart failure and 10 healthy volunteers. The coefficient of variation for TNF-alpha and IL-6 levels increased with time in patients, with the coefficient of variation in heart failure patients greatest for IL-6. The coefficient of variation in cytokine receptor levels was minimal and did not differ significantly between heart failure patients and control subjects. This study suggests that the sample size needed to show a statistically as well as biologically significant change in the circulating level of a

JACC Vol. 34, No. 7, 1999
December 1999:2068–71

given cytokine will vary depending on the specific cytokine studied and period of observation. The authors stated, for example, that to detect a 15% reduction of either circulating TNF-alpha or IL-6 levels during a 16-week period, at an alpha level of 0.05 and with a power of 80%, a sample size of 21 (for TNF-alpha) and 377 (for IL-6) would be required. Gullestad et al. (11) followed 75 patients with variables assessed at 10 and 32 weeks as compared with baseline.

If the observations made by Gullestad et al. (11) are confirmed, the implication that ACE inhibitors are pleiotropic in their beneficial effects in heart failure should come as no surprise, because heart failure is such a plastic clinical entity and ACE inhibitors have produced remarkably consistent benefits from trial to trial and in a wide range of patients and conditions. However, the issue of high doses versus low doses of ACE inhibitors must again be addressed. In contradistinction to diuretic agents, ACE inhibitors have not been, in large-scale clinical trials, titrated according to an individual's symptoms. Rather, target doses were picked and forced titration schemes developed (26). Target doses of these agents have generally been equated to 150 to 300 mg/day of captopril or 20 to 40 mg/day of enalapril. Unfortunately, when clinical practice patterns are analyzed, ACE inhibitors, when used, are prescribed at much lower doses (25 to 50 mg/day of captopril and 2.5 to 5.0 mg/day of enalapril) (27,28). However, as the Gullestad et al. study (11) and others demonstrate, higher doses of ACE inhibitors produce greater hemodynamic, neurohormonal, inflammatory cytokine, symptomatic and prognostic benefits than do lower doses. For example, Pacher et al. (29) demonstrated that high dose enalapril treatment proved superior to low dose treatment with respect to symptomatology, despite similar effects on hemodynamic variables and maximal exercise capacity. Levine et al. (30) demonstrated that up-titration of ACE inhibitors to high doses (when accompanied by nitrate therapy) was well tolerated and improved clinical status and left ventricular systolic function. This group subsequently demonstrated that up-titration of lisinopril to a mean dose of 55 mg/day (and isosorbide dinitrate dose up to a mean of 286 mg/day) resulted in significant reversal of left ventricular remodeling (31). Van Veldhuisen et al. (32) evaluated the long-acting ACE inhibitor, imidapril, in 244 patients randomized to receive 2.5, 5 or 10 mg/day. At three-month follow-up, higher doses were superior with respect to a more pronounced effect on exercise capacity and some neurohomones, but this did not seem to be related to the extent of suppression of plasma levels of converting enzyme. Importantly, these higher doses were reasonably well tolerated.

Perhaps the most convincing evidence about higher doses of ACE inhibitors comes from the Assessment of Treatment with Lisinopril And Survival (ATLAS) clinical trial (28,33,34). The ATLAS trial was designed to determine whether high doses of lisinopril would result in lower mortality and morbidity than lower doses in comprable patients. It was a large, randomized, double-blinded, multicenter, international trial (287 clinical centers in 19 countries) in patients with an ejection fraction ≤30% (NYHA functional class II, III or IV). Low dose lisinopril was defined as 2.5 to 5 mg/day and high dose 30 to 40 mg/day. The primary outcome evaluated was all-cause mortality, with secondary end points including cardiovascular mortality and morbidity. Patients were followed for an average of 3.5 years and over 3,000 individuals were randomized. By the end of the study, almost 45% of patients in the low dose group had died as compared with 43% in the high dose group, but this difference was not statistically significant ($p = 0.128$). In contrast, hospital admissions for congestive heart failure were reduced by 24% in the high dose lisinopril group ($p = 0.003$). In addition, the combined end point of all-cause mortality and cardiovascular morbidity was lower in the high dose group (84% vs. 80%, $p = 0.002$).

Another complementary but smaller study was done by Luzier et al. (35). This effort evaluated the relation of digoxin, diuretic agents and ACE inhibitors (and dose) to hospital readmission rates over a 36-month period. The ACE inhibitor dose response analysis used the discharge dose and converted this to enalapril equivalent doses, while adjusting for renal dysfunction. Interestingly, only 22% of those patients taking ACE inhibitors in this study of 314 patients received currently recommended doses of enalapril (20 mg/day or its equivalent) and 41% received <5 mg of enalapril (or its equivalent) per day. Time for readmission was increased when an ACE inhibitor was used overall in the study ($p = 0.002$), and these agents were the principal covariate of 90-day decreased readmission rates. However, readmission rates were not reduced when the daily dose was ≤5 mg of enalapril equivalents per day. When patients received daily doses >10 mg equivalents, the 90-day readmission rate was decreased by almost 30%, as compared with those receiving a diuretic agent or digoxin alone ($p < 0.05$). Similarly, Gattis et al. (36) explored ACE inhibitor doses in elderly patients with heart failure and noted them to be less than optimal, with low doses associated with more clinical events. None of these studies give insight into the mechanism of ACE inhibitors' differential effects based on dose, but they all are in concert with the findings of Gullestad et al. (11). From a pathophysiologic viewpoint, higher doses of ACE inhibitors make sense, and we have learned that much of the beneficial effects of these drugs may be unrelated to de facto hemodynamic changes. We must strive harder to clarify the nuances of ACE inhibitors' actions in heart failure. One cannot help but wonder whether ACE inhibitor cytokine modulating effects, if, indeed, they are present, would help with the headache associated with this challenge!

Reprint requests and correspondence: Dr. James B. Young, Kaufman Center for Heart Failure, The Cleveland Clinic Foundation, 9500 Euclid Avenue (Desk F-25), Cleveland, Ohio 44195. E-mail: youngj@cesmtp.ccf.org.

REFERENCES

1. Young J. Chronic heart failure management. In: Topol E, editor. Textbook of Cardiovascular Medicine. Philadelphia: Lippincott-Raven, 1998:2273–307.
2. Cohn JN, Franciosa JA. Vasodilator therapy of cardiac failure. N Engl J Med 1977;297:254–8.
3. Chatterjee K, Massie B, Rubin S, Gelberg H, Brundage BH, Ports TA. Long-term outpatient vasodilator therapy of congestive heart failure: consideration of agents at rest and during exercise. Am J Med 1978;65:135–45.
4. Cohn JN, Archibold DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. N Engl J Med 1986;314:1547–52.
5. 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.
6. 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.
7. 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.
8. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992;327:685–91.
9. Cohn JN. The management of chronic heart failure. N Engl J Med 1996;335:490–8.
10. Tsuyuki RT, Yusuf S, Rouleau JL, et al. Combination neurohumoral blockade with ACE inhibitors, angiotensin II antagonists, and beta blockers in patients with congestive heart failure: design of the Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) pilot study. Can J Med 1997;105:897–904.
11. Gullestad L, Aukrust P, Ueland T, et al. Effect of high- versus low-dose angiotensin converting enzyme inhibition on cytokine levels in chronic heart failure. J Am Coll Cardiol 1999;34:2061–7.
12. Mann DL, Young JB. Basic mechanisms in congestive heart failure: recognizing the role of pro-inflammatory cytokines. Chest 1994;105: 897–904.
13. Torre-Amione G, Bozkurt B, Deseval A, Mann DL. An overview of tumor necrosis factor alpha and the failing human heart. Curr Opin Cardiol 1999;14:206–10.
14. Francis GS. TNF alpha and heart failure: the differences between proof of a principle and hypothesis testing. Circulation 1999;99: 3213–4.
15. Mann DL. Inflammatory mediators in heart failure: homogeneity through heterogeneity. Lancet 1999;353:1812–3.
16. Bazzoni F, Beutler B. The tumor necrosis ligand and receptor families. N Engl J Med 1996;334:1717–25.
17. 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;323:236–41.
18. Matsumoi A, Yamada T, Suzuki H, Matoba Y, Sasayama S. Increased circulating cytokines in patients with myocarditis and cardiomyopathy. Br Heart J 1994;72:561–6.
19. Maury CPS, Teppo AM. Circulating tumor necrosis factor alpha (cachectin) in myocardial infarction. J Intern Med 1989;225:333–6.
20. Bassaran Y, Bassaran MW, Babacan KF, et al. Serum tumor necrosis factor levels in acute myocardial infarction and unstable angina pectoris. Angiology 1993;44:332–7.
21. Gurantz D, Cowling RT, Villarreal FJ, Greenberg BH. Tumor necrosis factor alpha upregulates angiotensin II type 1 receptors on cardiac fibroblasts. Circ Res 1999;85:272–9.
22. Moreira AL, Sampaio EP, Zmuidzinas A, Frindt P, Smith KA, Kaplan G. Thalidomide exerts its inhibitory action on tumor necrosis factor alpha by enhancing mRNA degradation. J Exp Med 1993;177: 1675–80.
23. Renick DG, Strieter RM, Lynch IJP, et al. In vivo dynamics of murine TNF alpha gene expression: kinetics of dexamethasone-induced suppression. Lab Invest 1989;60:766–71.
24. Deseval A, Bozkurt B, Seta Y, et al. Safety and efficacy of a soluble p75 tumor necrosis factor receptor (enbrel, etanacert) in patients with advanced heart failure. Circulation 1999;99:3224–6.
25. Dibbs Z, Thornby J, White BG, Mann DL. Natural variability of circulating levels of cytokines and cytokine receptors in patients with heart failure: implications for clinical trials. J Am Coll Cardiol 1999;33:1935–42.
26. Garg R, Yusuf S. Overview of randomized trials of angiotensin converting enzyme inhibitors on mortality and morbidity in patients with heart failure. JAMA 1995;18:1450–5.
27. Packer M. Do angiotensin converting enzyme inhibitors prolong life in patients with heart failure treated in clinical practice? J Am Coll Cardiol 1996;28:1323–7.
28. Hobbs RE. High or low doses of ACE inhibitors for heart failure? Clev Clin J Med 1998;65:539–42.
29. Pacher R, Stanek B, Globits S, et al. Effects of two different enalapril dosages on clinical, hemodynamic and neurohumoral response of patients with severe congestive heart failure. Eur Heart J 1996;17: 1223–32.
30. Levine TB, Levine AB, Keteyian SJ, Narins B, Lesch M. Reverse remodeling in heart failure with intensification of vasodilator therapy. Clin Cardiol 1997;20:697–702.
31. Levine AB, Muller C, Levine TB. Effects of high-dose lisinopril–isosorbide dinitrate on severe mitral regurgitation and heart failure remodeling. Am J Cardiol 1998;82:1299–1301.
32. Van Velduisen DK, Genth-Zotz S, Brouwer J, et al. High versus low dose ACE inhibition in chronic heart failure: a double blind, placebo controlled study on indapril. J Am Coll Cardiol 1998;32:1811–8.
33. Jackson G. ATLAS: High dose lisinopril is superior to low dose in heart failure. J Clin Pract 1998;52:139.
34. Husten L. ATLAS shows global undertreatment of heart failure. Lancet 1998;351:1035.
35. Luzier AB, Forrest A, Adelman M, Hawari FI, Schentag JJ, Izzo JL Jr. Impact of angiotensin-converting enzyme inhibitor underdosing on rehospitalization rates in congestive heart failure. Am J Cardiol 1998;82:465–9.
36. Gattis WA, Larsen RL, Hasselblad V, Bart BA, O'Connor CM. Is optimal angiotensin converting enzyme inhibitor dosing neglected in elderly patients with heart failure? Am Heart J 1998;136:43–8.