Exercise Tolerance as a Guide to Therapeutic Efficacy for Heart Failure
The Potential for Angiotensin Receptor Blockers

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The early trials of efficacy of therapy for heart failure focused on exercise tolerance as a guide to symptom relief. Patients with heart failure usually seek medical help because of an impairment of their exercise capacity, and it seemed reasonable to use quantitative assessment of this capacity to guide our therapeutic efforts. Indeed, early studies of nitrates and of captopril suggested a significant improvement in peak exercise capacity when these drugs were added to conventional therapy. The duration of these studies, which were designed to demonstrate short-term improvement, was usually 3 to 6 months.

Then why has exercise tolerance fallen out of favor in the continuing effort to document efficacy of therapy? A number of reasons can be cited. Peak exercise time during a progressively loaded test has a very subjective end point dependent on the motivation of both the patient and the examiner. The end point can be made more quantitative by the collection of expired gas to calculate peak oxygen consumption and to document that the subject surpassed the anaerobic threshold, but this adds considerable complexity to a multicenter study. Furthermore, demonstration of a statistically significant increase in exercise time does not necessarily mean that the patient feels better or can do more in his or her daily life, an end point that is far more pertinent to the therapeutic goal.

The magnitude of improvement in exercise time in most early drug trials was modest and variable, and it became apparent that responsiveness to therapy was more dependent on optimization of background diuretic therapy than on the efficacy of the experimental agent. For example, the dramatic exercise response to captopril in the initial controlled trial of 100 mg TID could have been related to the high dose used but has been more often attributed to the likelihood that this early study of severe heart failure evaluated patients who were inadequately diuresed. ACE inhibitors may normalize pulmonary capillary pressure if it is elevated. When diuretics have already normalized the pulmonary capillary pressure, the symptom response to vasodilator therapy may not be easily demonstrable. Indeed, a review of all the ACE inhibitor heart failure trials reveals that only two thirds were able to show an improvement in exercise capacity.

Another reason for skepticism about the utility of exercise testing—or indeed, any subjective end point in heart failure studies—is the recognition that the disease and its symptomatology progress over time. Does a 3- or 6-month study assess an improvement from baseline as a result of therapy or as a result of a slowing of progression of the disease? This distinction becomes especially important when one is attempting to translate short-term hemodynamic response into clinical efficacy. Furthermore, because mortality is substantial and nonmorbid end points therefore cannot be obtained in all patients entered into a study, the correction of intention-to-treat analysis for missing data points introduces biases that defy adjustment. The fallback position is to abandon the nonmorbid end points and use mortality and morbidity data as the guide to efficacy. One problem with this approach is that most of the patients entered into the trial will not contribute to this end point, which is confined to those who have suffered a protocol-defined event. It is then customary to define efficacy on the basis of the percent reduction in event rate, not on the magnitude of benefit in the entire population.

Initial morbidity and mortality trials revealed that these clinical end points were surprisingly more sensitive and reproducible than exercise tolerance testing. Consequently, morbidity and mortality have become the primary end points in most recent trials. The recognition that symptom relief remains an important independent outcome has led to the validation and application of quality-of-life assessments as a more global way to evaluate patient well-being than reliance on the vagaries of exercise time.

None of these trends in drug development should denigrate the value of quantitative exercise capacity as a potential guide to physiological efficacy of a therapeutic agent for heart failure. Therefore, the demonstration by Riegger and colleagues of a statistically significantly favorable effect of high-dose candesartan on exercise time in a 12-week study should be viewed as a useful documentation that the drug exerts a beneficial physiological effect in heart failure. The modest and variable benefit with regard to symptoms and New York Heart Association classification, despite the robust size of the study population, lends further credence to the concept that peak exercise capacity and quality of life cannot easily be equated. The two tend to vary in parallel in individuals with a striking treatment-induced effect, but noise in the exercise measurement tends to obliterate the

The opinions expressed in this editorial are not necessarily those of the editors or of the American Heart Association.

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relationship when changes are small. Furthermore, the well-known publication bias for positive trials and the recent recognition that short-term exercise or quality-of-life effects and long-term mortality effects may be contradictory\textsuperscript{12,13} should temper the interpretation of this positive candesartan exercise study.

Riegger and associates\textsuperscript{10} have clearly stated the preliminary nature of their studies. By precluding ACE inhibitors in this study population, they cannot contrast the magnitude of exercise improvement from candesartan with what may have been achieved with guideline-mandated ACE inhibitor therapy. They have not assessed the long-term effects of candesartan on morbidity and mortality, which is the end point for which ACE inhibitors have gained mandatory status. These patients were not treated with β-blockers, which are now also widely recommended because of their long-term efficacy.\textsuperscript{12}

The place of angiotensin receptor blockers in the therapy of heart failure will be established only after long-term trials are performed with or without the addition of ACE inhibitors and β-blockers. Fortunately, such trials are under way\textsuperscript{14,15} and should provide us with the necessary information to establish the proper future place for angiotensin receptor blockers in pharmacotherapy for heart failure.

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Key Words: Editorials ■ exercise ■ heart failure
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Circulation. 1999;100:2208-2209
doi: 10.1161/01.CIR.100.22.2208

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/100/22/2208

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