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Editorial Comment

How Should We Judge the Efficacy of Drug Therapy in Patients With Chronic Congestive Heart Failure? The Insights of Six Blind Men*

MILTON PACKER, MD, FACC

New York, New York

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind);
That each by observation
Might satisfy his mind.

John Godfrey Saxe
The Blind Men and the Elephant (1)

Major strides have been made during the last decade in the management of patients with congestive heart failure. We now have a variety of new inotropic and vasodilator drugs that can produce short- and long-term hemodynamic and clinical improvement in these patients with an acceptable frequency of adverse reactions (2). The changes produced by these new approaches, however, have generally been less dramatic than those that occurred when potent diuretics were first introduced in the management of this disorder. Although many patients experience marked relief of their disabling symptoms after institution of treatment with vasodilator and inotropic agents, the improvement in others is subtle and may only become apparent during prolonged therapy or when effective treatment is withdrawn. Such beneficial changes, although quite important, may be difficult to discern in a clinical setting where symptoms may be greatly influenced by variable compliance with diet and medications and by an unpredictable progression of the underlying disease.

How then are we to judge the efficacy of drug therapy in the patient with congestive heart failure? The problem not only is germane to the clinician who is caring for the individual patient, but is critical to the clinical investigator, who must develop rational end points that can be used in the design of studies to evaluate the utility of new therapeutic agents. Such trials form the basis of the approval of these drugs by governmental regulatory agencies charged with the responsibility for releasing only safe and *effective* drugs to the general public.

At first glance, it might appear that a number of approaches can be used to evaluate the status of patients with congestive heart failure. We may inquire about symptoms; we may assess clinically the degree of fluid retention; we may evaluate left ventricular function noninvasively by echocardiography or radionuclide ventriculography; we may perform invasive hemodynamic testing to measure cardiac output and ventricular filling pressures; we may measure functional capacity by treadmill or bicycle exercise testing; and we may attempt to evaluate the impact of treatment on the natural history of the disease. Which of these six approaches best reflects the efficacy of drug therapy? Or, like the six blind men describing different parts of the elephant, does each approach provide only a limited perspective of a highly complex pathophysiologic state that we cannot completely comprehend at the present time? The report by Leier and his colleagues (3) in this issue of the Journal helps to provide some insights into this important dilemma.

The First Blind Man: Symptoms as a Therapeutic End Point

Because congestive heart failure is a clinical syndrome, the most direct approach to its evaluation is to inquire about symptoms of dyspnea and fatigue at rest and on exertion and to estimate the degree of disability during the course of daily physical activity. These symptoms are then commonly classified according to a categorical scale, such as that of the New York Heart Association (4), and the efficacy of a therapeutic intervention is judged using each patient as his own historical control. Although simple, such a classification is not quantifiable, is subject to considerable interobserver variability and lacks adequate sensitivity to detect small but important changes in functional capacity. Furthermore, many patients seeing a physician or receiving a drug for the first time improve (in part) because they have entered a new therapeutic environment, which (by increasing the expectation of anticipated benefit) reduces anxiety concerning symptoms and reinforces compliance with recommendations concerning treatment that may have been previously made but ignored. The creation of such a therapeutic environment occurs commonly in clinical practice, but is greatly exaggerated in the setting of a formal research

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From the Division of Cardiology, Department of Medicine, Mount Sinai School of Medicine of The City University of New York, New York, New York. Dr. Packer is the recipient of Research Career Development Award K04-HL-01229 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

Address for reprints: Milton Packer, MD, Division of Cardiology, Mount Sinai Medical Center, One Gustave Levy Place, New York, New York 10029.

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trial, in which the personal attention provided to the patient reaches extreme levels. Such attention may explain why 20 to 30% of patients who enter heart failure trials show significant improvement with placebo therapy (5–7), as was the case in the study by Leier et al. (3). Consequently, the frequency of clinical improvement after a specific drug intervention is hard to evaluate (with confidence) in the absence of a placebo-treated group. Even when such a control group is available for purposes of comparison, the evaluation of symptoms remains a highly subjective matter that is greatly influenced by the underlying biases of both the patient and physician.

The Second Blind Man: Clinical Assessment of Fluid Retention

Because the syndrome of congestive heart failure is a sodium-avid state, it would seem logical to evaluate the efficacy of drug therapy by observing the patient for changes in signs of fluid retention, as can be assessed by physical examination, body weight and the detection of pulmonary congestion by chest radiography. Although changes in these clinical variables provide an important means of measuring the value of diuretic agents, they are not useful in measuring therapeutic benefits in patients treated with vasodilator and inotropic agents, which may produce symptomatic improvement without notable changes in sodium balance (8). Furthermore, most patients with heart failure undergo a therapeutic diuresis as part of an attempt to optimize conventional therapy before entry into a formal clinical trial; hence, pulmonary rales and peripheral edema are generally not present at the onset of therapy, even though patients may still have severe symptoms. Finally, the evaluation of fluid retention by physical and radiologic examination remains highly subjective and is not easily quantified. Any drug effect as assessed by these clinical variables may be particularly difficult to discern if the doses of concomitantly administered diuretics are altered in an effort to maintain body weight, as they were in the trial of Leier et al. (3).

The Third Blind Man: Noninvasive Measures of Left Ventricular Function

Because most patients with congestive heart failure have evidence of severely depressed left ventricular systolic function, it would seem logical to evaluate the efficacy of drug therapy by looking at changes in left ventricular performance during the course of treatment. This assessment can be performed by a variety of noninvasive techniques including echocardiography, radionuclide ventriculography and systolic time intervals. All three techniques are objective, quantifiable and reproducible; the first two techniques have particular appeal, because they provide a direct visual image of systolic ejection. Most importantly, these noninvasive measures have been shown to improve significantly during effective treatment in controlled trials (5,9,10) and remain unaltered during placebo therapy (10), as was the case in the present trial by Leier et al. (3).

Unfortunately, vasodilator and inotropic drugs may produce marked hemodynamic and clinical improvement in patients with congestive heart failure *without* a notable change in noninvasive indexes of left ventricular performance. Most of the changes seen in these noninvasive measures during effective treatment are quite small and fall within the range of error for many of these measurements (5,11); the benefits induced by therapy must be large in magnitude to elicit detectable changes in left ventricular function (12). Furthermore, conventional imaging techniques only reflect changes in ventricular volumes and in ventricular systolic ejection; they do not quantify alterations in mitral or aortic regurgitant flow or in ventricular diastolic function, both of which may contribute significantly to the hemodynamic improvement seen during effective treatment (13,14). Consequently, changes in noninvasive measures of left ventricular performance seen during the course of beneficial drug therapy have not been shown to correlate closely with observed changes in hemodynamic variables, clinical status or functional capacity (12,15,16). In fact, the left ventricular ejection fraction may increase significantly in patients with heart failure whose clinical state has *deteriorated* during treatment and who have fared worse than their placebo-treated counterparts (17).

The Fourth Blind Man: Invasive Hemodynamic Evaluation

Because most patients with severe heart failure have low values for cardiac output and elevated values for ventricular filling pressures at rest or during exercise, it would seem logical to evaluate the efficacy of therapeutic interventions based on their ability to correct the hemodynamic abnormalities seen in patients with this disorder. The measurement of conventional cardiocirculatory variables also permits the calculation of derived variables (for example, systemic vascular resistance), which may reflect the occurrence of specific pharmacologic events. Such hemodynamic evaluations require the performance of right heart catheterization, however, which carries its own risks and does not lend itself to repeated observations over prolonged periods of time. Nevertheless, when such serial measurements have been made in controlled trials, they have provided compelling evidence for drug efficacy, especially when similar benefits were not seen in a parallel group treated with placebo (10,18,19).

Pitfalls of hemodynamic measurements. Unfortunately, in the absence of a placebo-treated parallel group, clinicians and investigators cannot be certain that the hemodynamic changes seen after the administration of a new therapeutic agent represent a true drug effect. Spontaneous fluctuations in hemodynamic variables of small magnitude

are frequently seen in the absence of drug therapy and can be interpreted as reaching statistical (and biologic) significance, if postdrug effects are not assessed at fixed times and if threshold values (that exceed the level of spontaneous variability) are not used to rule out time-related rather than drug-related events (20). If the investigator defines a "peak effect" independently for *each* hemodynamic variable regardless of the time of occurrence, he creates a self-fulfilling prophecy that a true drug effect has indeed occurred. Even if uniform times and threshold values are used, hemodynamic changes mimicking a beneficial drug response may be seen in the absence of effective drug therapy, if measurements are performed immediately after right heart catheterization or after the ingestion of a normal meal (21,22). In particular, intravascular instrumentation appears to elicit notable systemic vasoconstriction (presumably related to overt or inapparent anxiety), which dissipates in 12 to 24 hours. If predrug measurements are performed during this immediate postcatheterization period, any subsequent measurements performed days, weeks or months later can be interpreted as showing beneficial effects, if such long-term measurements are compared with the initial artifactually vasoconstricted state; similar degrees of systemic vasoconstriction may not be provoked during a second invasive study (23). If such precautions are not taken, investigators may report the occurrence of sustained hemodynamic improvement in patients receiving ineffective treatment. Such precautions were taken in the study by Leier et al. (3), however, and thus, no sustained hemodynamic effects were noted in the placebo-treated group.

Initial versus long-term drug effects. The hemodynamic effects of first doses of the study drug were not reported by Leier et al. (3), although these were measured. Why not? There appears to be a very complex relation between the short- and the long-term effects of drugs used in the treatment of congestive heart failure (24–26). The immediate benefits seen with some agents may not be sustained during long-term treatment, because the pharmacologic actions of the drug become attenuated with time or because counteractive vasoconstrictor forces are activated by therapy. Conversely, some patients who fail to show any hemodynamic response to the initial administration of a new therapeutic agent may have gradual improvement with time, because prolonged exposure to the drug sets in motion changes that progressively enhance the responsiveness of the circulation to treatment (26). Consequently, because the long-term effects of therapy bear a variable and unpredictable relation to the initial response to treatment, the potential long-term efficacy of any therapeutic intervention cannot be assessed by testing the hemodynamic response to the first dose of a new drug (27).

Increased cardiac output as a marker of drug efficacy. Should any change toward normal hemodynamic values be considered a beneficial response in patients with congestive heart failure? Because a reduction in forward flow would appear to be one of the principal factors limiting the exercise tolerance of patients with severe heart failure (28), we might be more encouraged by a drug that produces increases in cardiac output and decreases in systemic vascular resistance than by a drug that only reduces ventricular filling pressures during long-term treatment. Previous studies (17) have shown, however, that increases in cardiac output and decreases in systemic vascular resistance at rest or during exercise do not parallel changes in clinical status. Hence, drugs that primarily affect the circulation in this fashion do not produce consistent clinical benefits in patients with severe chronic heart failure (6,17,29); conversely, drugs may improve functional capacity without producing an increase in cardiac output or a decrease in systemic vascular resistance at rest or during exercise (10). These concepts are underscored by the study of Leier et al. (3), whose patients showed little clinical benefit from the study drug, although most of them showed a sustained reduction in systemic vascular resistance at rest and during submaximal exercise during long-term treatment.

Decreased left ventricular filling pressure as a marker of drug efficacy. Should we then be more encouraged by a drug that produces a sustained decrease in ventricular filling pressures rather than a long-term increase in cardiac output? Because nearly all of the more newly developed therapeutic agents for the treatment of heart failure work (in part) by their ability to alter loading conditions in the failing left ventricle, they must all produce important changes in left ventricular end-diastolic volume, a common factor in the calculation of both preload and afterload. Insofar as changes in left ventricular filling pressure reflect changes in left ventricular volume, we might expect a reduction in these intracardiac pressures to provide a useful index of therapeutic efficacy. In our experience, those patients with severe chronic heart failure who have shown clinical improvement have generally also shown significant decreases in left ventricular filling pressure ($\geq$5 mm Hg) during long-term drug therapy (26,30,31). Such sustained decreases in left ventricular filling pressure at rest and during exercise seem to be sufficient in the absence of any change in cardiac output or in systemic vascular resistance to produce notable clinical benefits (10). In fact, the only three drugs that have been shown to produce consistent symptomatic improvement in patients with chronic heart failure in placebo-controlled trials (isosorbide dinitrate, captopril and enalapril [2,10,18,19]) all produce marked decreases in left ventricular filling pressures at rest and during exercise during long-term treatment. Therefore, it is not surprising that in the study by Leier et al. (3), ineffective therapy with indoramin failed to produce notable long-term decreases in left ventricular filling pressure in the majority of treated patients.

Can we then reasonably suggest that (in the absence of a placebo-treated group) a criterion of a 5 mm Hg or greater decrease in left ventricular filling pressure during long-term treatment be used as a measure of drug efficacy in patients

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with congestive heart failure, assuming that the appropriate methodologic precautions have been taken? Although the observation of such a hemodynamic change is encouraging and suggests the probability of an accompanying beneficial clinical response, this criterion is not uniformly paralleled by an improvement in symptoms in all patients or during treatment with all drugs (32). This suggests that other factors (such as physical conditioning, neurohormonal effects and drug toxicity) are also important in mediating changes in the clinical status of these severely ill patients.

The Fifth Blind Man: Objective Evaluation of Functional Capacity

Because patients with severe heart failure have a notable limitation of their functional capacity, it would seem logical to evaluate the efficacy of therapeutic interventions based on their ability to prolong the duration of tolerable exercise. This assessment can be performed by a variety of noninvasive techniques, the most common of which is the measurement of total exercise duration using a graded treadmill or bicycle exercise protocol. This approach is objective and quantifiable. Most importantly, exercise duration has been shown to improve significantly during effective treatment with vasodilator drugs in controlled clinical trials (5,8, 10,18,19,29).

Unfortunately, the duration of exercise in congestive heart failure is highly dependent on the motivation of both the patient and the physician. During routine clinical conditions, repeated testing predictably results in an improvement in exercise performance, in part due to the increased familiarity of the patient with the testing procedure and in part due to an increased willingness of the physician to encourage the patient to exercise to exhaustion. Such inadvertently submaximal efforts can in part be detected by the failure of the patient to achieve a respiratory gas exchange ratio greater than 1.0, indicating that lactate accumulation has not occurred and that exercise has ceased because of factors unrelated to circulatory function. If respiratory gas exchange is not measured, therefore, a notable improvement in exercise duration may follow the institution of placebo therapy and may be large enough to mimic a therapeutic drug response in the absence of effective treatment (6,7,33).

Maximal oxygen uptake as a marker of drug efficacy. The accurate measurement of respiratory gas exchange permits oxygen consumption to be measured directly and, thus, allows for the quantification of maximal exercise capacity by the determination of maximal oxygen uptake ($\dot{V}O_2$max). This variable ($\dot{V}O_2$max) has been proposed as a sensitive index for assessing the efficacy of drug therapy in patients with congestive heart failure (34). The accuracy of this measurement, however, requires that a true maximal effort has been extended by the patient; such a conclusion can be reached only if a plateau in oxygen uptake can be demonstrated despite further increments in exercise work load. Although such a plateau can be demonstrated in normal individuals, patients with congestive heart failure cannot achieve a plateau in oxygen uptake during graded exercise because they are limited by symptoms of dyspnea and fatigue (35,36). Even if one redefines $\dot{V}O_2$max as a failure of oxygen uptake to increase by more than 1 ml/kg per min with incremental work loads (34), patients tend to stop exercising at a new work load before the next measurement in oxygen uptake can be obtained; hence, it may be very difficult to show that steady state conditions with reference to oxygen uptake have been achieved (35). For this reason, the observed *peak* $\dot{V}O_2$ has been used by many investigators to quantify exercise capacity, but in patients with a markedly impaired exercise capacity, this measurement (which may be significantly influenced by patient motivation) may differ from the true $\dot{V}O_2$max by up to 25%; therefore, increases in peak $\dot{V}O_2$ up to 25% can occur with repeated exercise testing in such patients in the absence of effective therapy (35). This may explain the significant increase in peak $\dot{V}O_2$ seen in the patients treated with placebo in the study by Leier et al. (3).

Anaerobic threshold as a marker of drug efficacy. Because of the relative insensitivity of peak $\dot{V}O_2$ as an index of functional capacity in patients with congestive heart failure, several investigators have proposed the determination of anaerobic threshold (as determined by either the blood lactate or the ventilatory response to incremental exercise) for the assessment of the functional state in this disorder (34). Unfortunately, the point at which ventilation and carbon dioxide output increase disproportionate to oxygen uptake may be extremely difficult to define (36); similarly, blood lactate increases throughout exercise in patients with severe heart failure without a clearly identifiable threshold point. Both the lactate and ventilatory variables may change so gradually that it is left to the discretion of the physician to decide precisely when the anaerobic threshold has been achieved (37). The problem is made infinitely more complicated in the patient with a severely impaired peak $\dot{V}O_2$, in whom the initial work load of most exercise tests involves levels of oxygen consumption very close to or above the anaerobic threshold (36).

Submaximal exercise tests. The most serious limitation of all of these tests of functional capacity is that they are designed to evaluate exercise performance at maximal work loads, but daily activities do not generally require an energy expenditure in the maximal range. Hence, although drug therapy may be considered to be highly effective when accompanied by a dramatic improvement in maximal exercise performance, it is possible that clinical symptoms may be significantly ameliorated by drug treatment that does not increase maximal oxygen uptake but enhances exercise capacity at submaximal work loads that more realistically resemble routine physical effort. For this reason, submaximal

or endurance tests have been developed and applied to the evaluation of patients with congestive heart failure (35,38), but there is as yet little experience with these tests to determine their reproducibility, utility and validity.

The Sixth Blind Man: Survival as a Therapeutic End Point

Even if drug therapy decreases the symptoms of patients with congestive heart failure, the mortality of these patients remains extremely high and is directly related to the severity of the underlying disease. It would therefore seem logical to evaluate the efficacy of a new therapeutic intervention based on its ability to prolong survival. This end point is the most laudable goal in the treatment of the patient with congestive heart failure; it is also objective, quantifiable and not readily subject to observer bias. Precisely such an approach has recently been used to demonstrate the utility of the direct-acting vasodilator drugs, hydralazine and isosorbide dinitrate (39), in the management of congestive heart failure. This drug combination had previously not been shown to decrease symptoms or reduce signs of fluid retention or result in improved noninvasive measures of left ventricular performance or maximal exercise capacity in this disorder.

Unfortunately, until surrogate end points for survival can be developed, the evaluation of the impact of any therapeutic intervention on mortality can be assessed only by the performance of a randomized, placebo-controlled trial in several thousand patients. Such trials are complex and expensive, however, and often provide little data concerning pathophysiologic mechanisms. Nevertheless, they are necessary to address the issue of survival, because the individual clinician cannot evaluate the impact of treatment on mortality in the individual patient. Yet, the clinical data derived from such trials may be difficult to translate into practice, because any therapeutic intervention that prolongs life but fails to simultaneously lessen symptoms would remain an unsatisfactory approach to the total management of the severely limited patient with chronic heart failure.

Conclusions: The Synthesis of the Elephant

Which of the six approaches outlined provides the best reflection of drug efficacy in the patient with severe chronic heart failure? Each approach offers an important goal for drug therapy, because each time the physician administers a new drug for the treatment of heart failure, he tries to reduce symptoms, to ameliorate fluid retention, to improve invasive and noninvasive measures of left ventricular performance, to enhance functional capacity and to prolong life. Each time the clinical investigator evaluates a new drug for the treatment of heart failure, he attempts to demonstrate its value with respect to as many of these therapeutic end points as is possible, preferably in the context of a placebo-controlled trial. Unfortunately, each approach carries with it important conceptual and methodologic limitations and, thus, provides only an incomplete picture of a highly complex and multifaceted pathophysiologic state. Therefore, if we attempt (in our present state of knowledge) to consider the information derived from each of these viewpoints as a whole, the composite perspective is frequently confusing and may be frankly contradictory.

Such confusion will be clarified in the future only by efforts directed toward determining the *relation* among these six therapeutic end points. What hemodynamic events are responsible for the symptoms and exercise intolerance of these patients? Do changes in left ventricular performance or in exercise capacity translate into alterations in survival? Can other therapeutic end points (that is, neurohormonal events) provide an important mechanistic link among these six approaches? Even partial answers to these questions will offer important pathophysiologic insights into understanding the syndrome of congestive heart failure during the next decade.

> In the land of the blind, the
> one-eyed man is king.
>
> *Scottish proverb*

References

1. Saxe JG. Poems. Boston: Houghton Mifflin, 1852.
2. Packer M. Vasodilator and inotropic therapy for severe chronic heart failure: passion and skepticism. J Am Coll Cardiol 1983;2:841–52.
3. Leier CV, Binkley PF, Randolph PH, Unverferth DV. Chronic indoramin therapy in congestive heart failure: a double-blind, randomized, parallel placebo-controlled trial. J Am Coll Cardiol 1987;9:426–32.
4. The Criteria Committee of the New York Heart Association. Diseases of the Heart and Blood Vessels: Nomenclature and Criteria for Diagnosis. 7th ed. Boston: Little, Brown, 1973:286.
5. Captopril Multicenter Research Group. A placebo-controlled trial of captopril in refractory chronic congestive heart failure. J Am Coll Cardiol 1983;2:755–63.
6. Franciosa JA, Weber KT, Levine TB, et al. Hydralazine in the long-term treatment of chronic heart failure: lack of difference from placebo. Am Heart J 1982;104:587–94.
7. Massie B, Bourassa M, DiBianco R, et al. Long-term oral amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial. Circulation 1985;71:963–71.
8. Cleland JGF, Dargie HJ, Ball SG, et al. Effects of enalapril in heart failure: a double-blind study of effects in exercise performance, renal function, hormones, and metabolic state. Br Heart J 1985;54:305–12.
9. Colucci WS, Wynne J, Holman BL, Braunwald E. Long-term therapy of heart failure with prazosin: a randomized double-blind trial. Am J Cardiol 1980;45:337–44.
10. Leier CV, Huss PM, Magorien RD, Unverferth DV. Improved exercise capacity and differing arterial and venous tolerance during chronic isosorbide dinitrate therapy for congestive heart failure. Circulation 1983;67:817–22.
11. DeMaria AN, Vismara LA, Auditore K, Amsterdam EA, Zelis R, Mason DT. Effects of nitroglycerin on left ventricular cavitary size and cardiac performance determined by ultrasound in man. Am J Med 1974;57:754–60.
12. Firth BG, Dehmer GJ, Markham RV, Willerson JT, Hillis LD. Assessment of vasodilator therapy in patients with severe congestive heart

failure: limitations of measurements of left ventricular ejection fraction and volumes. Am J Cardiol 1982;50:954–9.

13. Urquhart J, Packer M, Patterson R, Horowitz SF, Micelli K, Gorlin R. Quantification of valvular regurgitation before and after medical and surgical therapy by radionuclide angiography (abstr). Am J Cardiol 1980;47:498.
14. Brodie BR, Grossman W, Mann T, McLaurin LP. Effects of sodium nitroprusside on left ventricular diastolic pressure-volume relations. J Clin Invest 1977;59:59–68.
15. Engler R, Ray R, Higgins CB, et al. Clinical assessment and follow-up of functional capacity in patients with chronic congestive cardiomyopathy. Am J Cardiol 1982;49:1832–7.
16. Franciosa JA, Park M, Levine TB. Lack of correlation between exercise capacity and indexes of resting left ventricular performance in heart failure. Am J Cardiol 1981;47:33–9.
17. Franciosa JA, Jordan RA, Wilen MM, Leddy CL. Minoxidil in patients with chronic left heart failure: contrasting hemodynamic and clinical effects in a controlled trial. Circulation 1984;70:63–8.
18. Kramer BL, Massie BM, Topic N. Controlled trial of captopril in chronic heart failure: a rest and exercise hemodynamic study. Circulation 1983;67:807–16.
19. Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. Circulation 1984;70:271–8.
20. McKay CR, Nana M, Kawanishi DT, et al. Importance of internal controls, statistical methods, and side effects in short-term trials of vasodilators: a study of hydralazine kinetics in patients with aortic regurgitation. Circulation 1985;72:865–72.
21. Packer M, Medina N, Yushak M. Hemodynamic changes mimicking a vasodilator drug response in the absence of drug therapy after right heart catheterization in patients with chronic heart failure. Circulation 1985;71:761–6.
22. Cornyn JW, Massie BM, Unverferth DV, Leier CV. Hemodynamic changes after meals and placebo treatment in chronic congestive heart failure. Am J Cardiol 1986;57:238–41.
23. Packer M, Medina N, Yushak M. Spontaneous hemodynamic changes mimicking a vasodilator drug response in severe chronic heart failure in the absence of drug therapy (abstr). J Am Coll Cardiol 1985;5:461.
24. Franciosa JA, Dunkam WB, Leddy CL. Hemodynamic effects of vasodilators and long-term response in heart failure. J Am Coll Cardiol 1984;3:1521–30.
25. Massie BM, Kramer BL, Topic N. Lack of relationship between short-term hemodynamic effects of captopril and subsequent clinical responses. Circulation 1984;69:1135–41.
26. Packer M, Medina N, Yushak M, Meller J. Hemodynamic patterns of response during long-term captopril therapy for severe chronic heart failure. Circulation 1983;68:803–12.
27. Packer M, Medina N, Yushak M. Comparative hemodynamic and clinical effects of long-term treatment with prazosin and captopril for severe chronic congestive heart failure secondary to either coronary artery disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1986;57:1323–8.
28. Wilson JR, Ferraro N. Exercise intolerance in patients with chronic left heart failure: relation to oxygen transport and ventilatory abnormalities. Am J Cardiol 1983;51:1358–63.
29. Agostoni PG, de Cesare N, Doria E, Polese A, Tamborini G, Guazzi MD. Afterload reduction: a comparison of captopril and nifedipine in dilated cardiomyopathy. Br Heart J 1986;55:391–9.
30. Packer M, Meller J, Medina N, Gorlin R, Herman MV. Importance of left ventricular chamber size in determining the response to hydralazine in severe chronic heart failure. N Engl J Med 1980;303:250–5.
31. Packer M, Medina N, Yushak M. Role of the renin-angiotensin system in the development of hemodynamic and clinical tolerance to long-term prazosin therapy in patients with severe chronic heart failure. J Am Coll Cardiol 1986;7:671–80.
32. Packer M, Medina N, Yushak M. Hemodynamic and clinical limitations of long-term inotropic therapy with amrinone in patients with severe chronic heart failure. Circulation 1984;70:1038–47.
33. Franciosa JA, the Captopril-Digitalis Research Group. Contribution of metabolic measurements to exercise testing in congestive heart failure (abstr). J Am Coll Cardiol 1985;5:513.
34. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Oxygen utilization and ventilation during exercise in patients with chronic cardiac failure. Circulation 1982;65:1213–23.
35. Le Jemtel TH, Mancini D, Gumbardo D, Chadwick B. Pitfalls and limitations of "maximal" oxygen uptake as an index of cardiovascular functional capacity in patients with chronic heart failure. Heart Failure 1985;1:112–24.
36. Wilson JR, Fink LI, Ferraro N, Dunkman WB, Jones RA. Use of maximal bicycle exercise testing with respiratory gas analysis to assess exercise performance in patients with congestive heart failure secondary to coronary artery disease or to idiopathic dilated cardiomyopathy. Am J Cardiol 1986;58:601–6.
37. Yeh MP, Reed M, Gardner M, et al. "Anaerobic threshold": problems of determination and validation. J Appl Physiol 1983;55:1178–86.
38. Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walking test for assessing exercise capacity in chronic heart failure. Br Med J 1986;292:653–5.
39. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration cooperative study (V-HeFT). N Engl J Med 1986;314:1547–53.