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CONGESTIVE HEART FAILURE

Proceedings of the Symposium on New Drugs and Devices
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PREFACE

About 2.5 million individuals have congestive heart failure in the United States with over 400,000 new cases expected annually. Congestive heart failure also is one of the commonest causes for hospital admissions accounting for over 5 million hospital days per year. Despite the early recognition of this condition and active medical research into both mechanisms and therapy, prognosis continues to remain dismal with less than a 50% expected five year survival. In the last decade we have seen many new medical and therapeutic options for patients with congestive heart failure which extend beyond the use of bed rest, sodium restriction, digitalis and diuretics. These include vasodilators of a variety of types including the angiotensin conventional enzyme (ACE) inhibitors. Also, many new inotropes are under active investigation both in oral and intravenous forms.

In March of 1984 a survey of over 5000 physicians was performed under the auspices of the American Heart Association (reported in: JACC 8:966, 1986). That survey showed that there was no universally accepted definition for congestive heart failure and that a wide spectrum of diagnostic criteria for this common condition existed even among academic cardiologists. There was no clear standard as to even the most basic treatment of congestive heart failure. For example, exercise restriction was recommended by 19% of physicians, 31% recommended no change in activity, and 50% either light exercise or an exercise conditioning program. A similar variability existed in the restriction of sodium. In regards to initial medical therapy for congestive heart failure in patients with normal sinus rhythm,

53% of physicians used a diuretic alone, 7% digitalis alone, 30% a combination of digitalis and diuretics and only 9% used vasodilator therapy alone or in combination with other treatment. Interestingly, 67% of physicians felt that digitalis was effective in increasing exercise tolerance in patients with congestive heart failure yet only 7% gave digitalis alone as initial therapy. Only 50% of physicians were using vasodilators as therapy in patients with class III congestive heart failure. Most physicians felt that medical treatment of congestive heart failure decreased symptoms and increased exercise tolerance but few believed that mortality was altered.

Therefore it is not surprising that the Food and Drug Administration has not offered specific guidelines for the evaluation of new agents to control congestive heart failure. In performing clinical trials many basic issues remain unclear as to the safety and efficacy of anti-heart failure drugs. For example, what is the best definition to define congestive heart failure for clinical trials? What is the best means of measuring left ventricular function? What are the end points to determine efficacy for anti-heart failure drugs? Is a change in mortality a necessary endpoint? What measures of safety should be evaluated?

These and other questions were addressed at the Seventh Annual Symposium on New Drugs and Devices which brings together members from the Cardio-Renal Division of the Food and Drug Administration, academic investigators from the United States and abroad, and pharmaceutical researchers. This forum allows for free communication between these three groups.

The following chapters represent initial position statements by academic investigators and members of the Food and Drug Administration followed by discussion sections in which the participants were able to debate the various issues with the hope of arriving at a concensus. While no unanimous concensus was expected to evolve, the discussions clearly detailed the positions of the various groups. Thus, we expect this book to be useful, not only to investigators and regulators, but also to those interested in the current status of the various issues involved in the management of patients with congestive heart failure.

I. EPIDEMIOLOGY, THERAPEUTIC ENDPOINTS

1

THE PUBLIC HEALTH AND CLINICAL IMPLICATIONS OF THE NATIONAL INCREASE IN CONGESTIVE HEART FAILURE

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[A]. Congestive Heart Failure - The Public Health Problem

The last two decades have witnessed a substantial decline in mortality due to myocardial infarction and stroke. However, during a similar period, data obtained from the National Center for Health Statistics indicate that the number of deaths due to congestive heart failure (CHF) has increased more than four-fold; for example, the number of deaths in which CHF was considered to be the underlying cause increased from about 6000 in 1955 to over 30,000 by 1982. There was a parallel increase in the number of deaths in which CHF was considered to be a contributing cause, from 51,000 in 1955 to about 246,000 in 1982. Although a substantial part of this increase can be explained by the aging of the population, the age-adjusted death rates also show a two-fold increase. For example, the age adjusted death rates, where CHF was the underlying cause, increased from 3.5/100,000 in 1968 to about 7.5/100,000 by 1984. The incidence of CHF and deaths due to CHF increased exponentially with age in both sexes and all races. However for any specific age group, CHF mortality is about 1.6 times commoner in men and about two to three times commoner in blacks compared to whites.

For the U.S. population as a whole, the age-adjusted death rates for CHF have increased; however, this pattern is not shared by all age and race groups. For example, for the period 1968-78, age-adjusted death rates increased by 21%. However, during this period blacks experienced a 16% decline and whites, a 32% increase.

These changes were similar in males and females. In both racial groups, there was a marked decline in CHF mortality in younger age groups, whereas in older are groups there were increases. However, in whites the decline in CHF mortality was observed only up to the age group 45-54, whereas in blacks the decline was observed even among the 65-74 year group. While it is possible that the decline in CHF in blacks might reflect success in the treatment of hypertension, the decline in the incidence of strokes is similar for all racial groups and all age-groups, indicating that the situation for CHF might be more complex and influenced by different factors.

Paralleling the increase in deaths from CHF, the rate of hospitalization for CHF has shown a marked increase. For example, the number of hospital discharges where CHF was the first listed diagnosis increased from about 130,000 in 1970 to 456,000 by 1984, thereby becoming the commonest DRG in the population over 65 years of age. It is difficult to assess whether this increase involves any specific etiologies; but available data from National Hospital Discharge Statistics indicate a substantial increase in hospitalizations for cardiomyopathy (eg. first listed diagnosis of cardiomyopathy increased from about 8,000 in 1970 to 48,000 by 1981). However, these data should be cautiously interpreted because classification into various subcategories based on Hospital Discharge data may not be entirely reliable. While the number of days that patients spend in hospital has been declining, patients with a diagnosis of CHF accounted for 3.83 million hospital days in 1984. Applefeld estimates that the in-patient costs of treating patients with CHF was approximately 2 to 3 billion dollars in 1981[1] with costs likely to be higher for 1986.

Drugs that are used to treat patients with heart failure, such as diuretics and cardiac glycosides, are very commonly prescribed. For example, there were 26.7 million prescriptions for thiazide diuretics (the most commonly prescribed group of drugs in U.S.), 12.4 million prescriptions for digitalis (3rd most common) and 10.8 million prescriptions for Lasix (furosemide) (4th most common) in 1981. While the proportion of thiazide use for CHF is not known, Lasix and digitalis are likely to have been

used predominatly in CHF patients. The out-patient costs of the treatment of these patients is likely to be several hundreds of millions of dollars.

[B]. Congestive Heart Failure - The Clinical Problem

Once patients develop CHF, their subsequent prognosis is poor. For example, in the Framingham study about 80% of men over the age of 45 years with a diagnosis of CHF had died within 10 years.[2] Furthermore, this mortality rate was about twice that of patients who had developed myocardial infarction or 4 times higher than the mortality for the total population. The grim prognosis of CHF patients has been confirmed in a number of clinical studies (Table) [2,10] and varies from about 15% in the first year in the CASS Registry [3] to as high as 48% in NYHA Class IV patients in the study by Wilson et al. [4] Data from the CASS Registry and the V-HEFT [5] indicate that prognosis is worse among patients with more severe clinical classes of CHF and among those with lower ejection fraction. Further, several studies indicate that patients who have underlying coronary artery disease have a poorer prognosis compared to those with idiopathic cardiomyopathy.[5,6] While several studies have tried to identify whether other variables (eg. arrhythmias, catecholamines) have independent prognostic value, the results of these studies have been conflicting. This may be due, at least in part, to the small size of the studies, but may also reflect the high degree of correlation between the different variables, so that reliable distinction of factors that are truly independent, by statistical analyses may not be possible.

TABLE: Mortality Rates in CHF Patients in Nine Studies

		1 Year	3 Years	5 Years
[A].	Community Studies			
	1. McKee '71[2] (N=142) Males:	20%	45%	61%
	Females:	14%	32%	43%
[B].	Data Registry			
	1. Coronary Artery Surgery Study '82[3] + personal communication (N=2,388)	16%	29%	40%
[C].	Trials (Moderate CHF)			
	1. V-HEFT 86[5] (N=273)	20%	47%	-

[D]. Hospital Studies (Moderate or Severe CHF)

1.	Schwartz '84[7] (N=68)	-	33%	-
2.	Fuster '81[8] (N=104)	25%	50%	65%
3.	Wilson '83[4] (N=77)	48%	70%	about 100% (2 years)
4.	Massie '81 [9] (N=56)	37%	-	-
5.	Franciosa '83 [6](N=182)	34%	75%	-
6.	Unverferth '84[10](N=61)	35%	-	-

Conclusions and Implications

CHF is a major and growing public health problem. This increase is only partly explained by the aging of the population, since age-standardized death rates have also been rising. Once overt CHF has developed the prognosis of patients is generally poor with about 10% to 15% of all patients dying each year. There is an urgent need to evaluate the effects of current and future treatments on survival in such patients. Even modest reductions or increases in mortality (eg 10%) can result in prolonging or shortening several tens of thousands of lives in the Western world each year. Further, measures to prevent the development of CHF should also be explored. The Studies of Left Ventricular Dysfunction is such a research program that aims to evaluate whether treatment with an angiotensin converting enzyme inhibitor prolongs survival and prevents the progression of CHF in patients with left ventricular dysfunction regardless of the presence or absence of symptoms of overt heart failure.[11]

REFERENCES

1. Applefeld MM: Chronic Congestive Heart Failure: Where have we been? Where are we heading? Am J Med 80 Suppl 2B: 73-77, 1986.
2. McKee PA, Castelli WP, McNamara PM, et al: The natural history of congestive heart failure: The Framingham Study. N Engl J Med 285: 1441-1446, 1971.
3. Fisher LD, Alderman EL, Mock MB, Chaitman BR, Ringqvist I, Ryan TJ, Levine F, Kaiser GC, Schloss M, Killip T, Oberman A, Litwin P: Statistical Considerations in Evaluating Treatment of Advanced Congestive heart failure. In Congestive Heart Failure. Ed Braunwald E, Mock MB and Watson JT: p 357-366. Grune and Stratton Inc., 1982

4. Wilson JR, Schwartz JS, St. John-Sutton M, et al: Prognosis in severe heart failure: Relation to hemodynamic measurements and ventricular ectopic activity. J Amer Coll Cardiol 2: 403-410, 1983.
5. Cohn JN, Archibald DG, Ziesche S, et al: Effect of vasodilator therapy on mortality in chronic congestive heart failure. N Engl J Med 314: 1547-1552, 1986.
6. Franciosa JA, Wilen M, Ziesche S and Cohn JN: Survival in Men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 51: 831-835, 1983.
7. Schwarz F, Mall G, Zebe H, et al: Determinants of survival in patients with congestive cardiomyopathy: quantitative morphologic findings and left ventricular hemodynamics. Circulation 70: 923-928, 1984.
8. Fuster V, Gersh BJ, Giuliani ER, et al: The Natural History of Idiopathic Dilated Cardiomyopathy. Am J Cardiol 47: 525-531, 1981.
9. Massie B, Ports T, Chatterjee K, et al: Long-term vasodilator therapy for heart failure: Clinical Response and its relationship to hemodynamic measurements. Circulation 63: 269-278, 1981.
10. Unverferth DV, Magorien RD, Moeschberg ML, et al: Factors influencing the one-year mortality of dilated carrdiomyopathy. Am J Cardiol 54: 147-152, 1984.
11. Studies of Left Ventricular Dysfunction - Protocol, 1986.

2

THERAPEUTIC ENDPOINTS IN THE TREATMENT OF CONGESTIVE HEART FAILURE WITH SYSTOLIC DYSFUNCTION

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The definition and successful use of therapeutic endpoints in the treatment of congestive heart failure has been fraught with many difficulties, not the least of which are an adequate understanding of the etiology of the underlying process of myocardial failure, a dissociation of various endpoints from one another, such as symptomatology and mortality and an inability to define the factors which lead to progression of the primary disease.

The etiology of the underlying myocardial disease leading ultimately to congestive heart failure remains complex and poorly understood (1). In coronary artery disease, which in its later stages contributes approximately 60% of patients with congestive failure, the initiating process is segmental loss of myocardial tissue. Added to this may be subtle and variable abnormalities of contraction related to transiently ischemic muscle. Once tissue has been lost in the process of acute myocardial infarction, segmental fibrosis ensues with reactive hypertrophy occurring in the remaining myocardium. The extent of the hypertrophic process in the remaining part of the heart is directly related to the amount of tissue that is lost (2). Progressive hypertrophy may ultimately lead to a further decrease in myocardial function if the results of pressure overloads are taken as a model for such changes. This hypertrophied myocardium is generally characterized mechanically by a slowing of the contractile rate and a decrease in rates of myocardial relaxation, providing for not only systolic, but diastolic dysfunction of the heart (3). The factors which lead to this deterioration secondary to reactive hypertrophy are not at all

clear and what may alter the course of these events has not been determined.

Moreover, the changes in mechanical behavior resulting from this reactive hypertrophy due to loss of myocardium as contrasted with pressure overload induced hypertrophy have not been delineated. Further, effects of time or the extent of hypertrophy on the process are also unknown. Nevertheless, clinically, if the extent of loss of myocardium is great enough, what is initiated by acute infarction ultimately results in a dilated hypertrophic cardiomyopathy. The next major cause of myocardial failure "idiopathic cardiomyopathy or 'dilated cardiomyopathy". This clinical condition is characterized by focal and diffuse wall fibrosis where there has been loss of myocardial cells, combined with reactive hypertrophy in the remaining heart muscle which occurs in response to this tissue loss. The ventricle is dilated with generalized reduction of systolic wall motion. The initiating process that leads to these abnormalities has not been defined but animal data would suggest that there are abnormalities in the handling of calcium by myocardial cells as well as abnormalities in the microvasculature in the ventricular wall, so that focal microvascular spasm and ischemia may occur (1). In the presence of myocardial cells that have abnormal cell membranes and may be unable to tolerate ischemic events, calcium overloading has been theorized with subsequent cell death. Heart failure can also ensue after extensive pressure and volume overloads which result in either severe hypertrophy or ventricular dilatation from obligatory volume overloads. While these primary events lead to the initiation of myocardial failure evolving from different starting points, they all ultimately produce limitations in cardiac function that result in reduced cardiac output on demand and elevated central filling pressures. During earlier phases of the disease process, hypertrophy of the ventricular wall, combined with fibrosis leading to delayed relaxation and slowed ventricular filling may result in elevated filling pressures before systolic contraction is significantly reduced. Such diastolic dysfunction will be amplified by tachycardia and may be very disabling with

severe symptomatic limitation (4). Nevertheless, its prognosis and therapy are greatly different from that of systolic dysfunction.

How central events are connected to peripheral blood flow maldistribution and limitation is poorly understood. Nevertheless, once heart failure is established, it is clear that there is a limitation to cardiac output on demand with limitations in augmentation of peripheral blood flow in response to metabolic need. At some poorly defined point, sodium accumulation with edema also ensues, mediated by vascular and hormonal changes. Thus, there is augmentation of the sympathetic nervous system's activity, increases in the activity of the renin angiotensin system, and increasing vasoconstriction of the peripheral vasculature which is not hormonally dependent during maximum exercise (5,6). Elevation in aldosterone secretion occur and sodium retention is commonly seen. Ultimately, these limitations of peripheral blood flow with retention of salt and limited dilatation in response to muscular exercise produce the peripheral syndrome of congestive heart failure.

From what has been described above there are two phenomenon proceeding simultaneously: 1) the decrease in myocardial function evolving into myocardial failure; and, 2) alterations in the peripheral circulation with salt retention evolving into congestive heart failure (7). In these two events one sees one of the first dilemmas in therapeutic endpoints. To begin with, in congestive heart failure mortality rate appears to be well predicted by ejection fraction (8), which is a fairly reliable indicator of systolic left ventricular and myocardial function. However, severity of clinical heart failure as defined by symptoms is a poor predictor of mortality (9), although Class IV (NY Heart Assoc. patients) will most likely demonstrate an ejection fraction less than 20%. Thus, Class I has a more benign course than Class IV, but Class II and III are not separable in terms of mortality with any precision. There is not only a poor correlation of clinical class and ejection exercise tolerance, but there is little or no correlation between the two over a period of time. Furthermore, quality of life, well being of the patient and clinical class also do not correlate closely with

exercise tolerance. Thus, one has the initial dilemma that ejection fraction, which reflects contractility of the myocardium, predicts mortality, but does not correlate with how well the patient is doing from a symptomatic point of view or with exercise performance (10,11). Alternatively, symptoms are not directly correlated with myocardial dysfunction or its changes. Indeed, with some therapeutic interventions, improvement in the patient's symptoms may occur as demonstrated by improved exercise tolerance while left ventricular dilatation progresses inexorably with an ultimate reduction of the ejection fraction and resultant death (12). Accordingly, if the ultimate aim is to reduce mortality, an impact must be made on ventricular function with preservation of the myocardium (13). On the other hand, symptomatic improvement of the patient relies on an improvement in the peripheral circulation and enhancement in the ability of the patient to handle the salt load which has little to do with survival. Once these major dilemmas are recognized, one can then proceed to discuss the possibilities of at least evaluating the process in its evolution both relative to what the heart is doing as well as what changes are occurring in the periphery.

Acutely, efficacy is characterized by hemodynamic responses considered to be salutory, namely, an increase in cardiac output accompanied by a decrease in central filling pressures, and occurring if possible, with little change in heart rate or blood pressure. A decrease in blood pressure if serving to reduce afterload may also be salutary as long as symptomatic hypotension does not occur. Although these acute effects are needed to establish acute efficacy, they do not predict longer term efficacy in terms of improved exercise performance, enhanced clinical status, survival or indeed, maintained hemodynamic benefits (14). Nevertheless, with an acute problem of pulmonary edema where some reversible process is involved, efficacy can be measured in terms of these shorter term therapeutic goals.

Survival remains a centrally important therapeutic endpoint in heart failure given the fact that severe congestive heart failure is associated with a 50% mortality per year and this mortality has

not been substantially altered by current therapeutic modalities (15). If heart failure is mild and/or mostly due to diastolic dysfunction, the survival curve may be moved more substantially to the right especially when therapy is initiated at an earlier stage of the disease (16). However, the ultimate demise of the patient appears still to be predicated by the nature of the primary process rather than by the intercurrent therapy.

As noted, survival can be related to ejection fraction which provides some insight into staging of disease (8). Ejection fraction may be measured in many ways both invasively and non-invasively and the choice of methodology is largely one of convenience. Moreover, measurements of end diastolic dimension and end systolic dimension give similar information. Thus, when the end systolic dimension is enlarged, the end diastolic volume is also increased, and with the same level of stroke volume, the ejection fraction must fall. Thus, the simple measurement of end diastolic dimension may be adequate for tracking patients with congestive heart failure over a period of time relative to the status of their myocardium. Since the ventricular wall thickness does not change appreciably over and above the moderate thickening of hypertrophy, an increase in end diastolic and end systolic dimension indicates an augmentation of ventricular wall tension for any given pressure even if nothing else has occurred. Thus, dilatation per se places a further detrimental load upon the heart and both indicates and causes further deterioration of the ventricle as a pump. Mitral regurgitation resulting from ventricular dilatation will further complicate the problem (17).

The relation between ejection fraction and mortality may be further refined by other measurements which reflect the interaction of the limited cardiac function with the peripheral circulation including neurohumoral background or serum sodium levels (18). However, these measurements may well be derivative of the problem and not central. Thus, the measurement of norepinephrine has demonstrated that those with very high levels are more likely to have an early demise (19). Unfortunately, the

level of norepinephrine reflects the hemodynamic competence of the patient in general and even where this declines in the face of therapy, no benefit has been demonstrated relative to mortality (20). Another issue complicating mortality is severe ventricular arrhythmias. Here again, the severity of the arrhythmia and its outcome is predicated on the underlying ventricular function and has been associated with enhanced mortality, but therapeutic effects to alter this point have not been notably successful.

Cardiac function relative to time and in response to medication provides another therapeutic endpoint and, as mentioned above, this therapeutic endpoint is commonly coupled with survival. While multiple indices of contractility can be looked at, those related to initial size of the heart (end diastolic volume) and end systolic volume appear most appropriate and one can track the diastolic size of the heart as an index of progression of myocardial disease. Asynchronous contraction may affect absolute measurements and may also vitiate relative changes. Since wall shortening is inversely related to load, alterations in impedance will also alter such measurements, independent of fundamental changes in ventricular contractility. These findings are further complicated by the fact that mitral regurgitation is highly dependent on the ventricular size and thus, merely augmenting ventricular size may lead to further cardiac decompensation. It is thus important to track alterations in cardiac size in relation to the natural course of disease and relative to therapeutic interventions in order to assess what may be a useful intervention. This will need to be done at various stages of disease and the rates of progression relative to cardiac dimensions and time has not been assessed in order to provide a framework for predictability.

Quality of life reflects the multiple parameters that impinge on the patient's sense of well being and ability to function. Detailed questionnaires (21) are difficult to define and utilize and are not well correlated with exercise performance. As noted above, although exercise performance gives some sense of the limitation which the patient has, it is important to define what one means by exercise performance. This will be dealt with more in the

subsequent presentation by Dr. LeJemtel, but clearly tests must differentiate between peak power ie. maximum $\dot{V}_{O_2}$ and endurance which is the capacity to maintain a substantial load in a stable state. Endurance is commonly associated with capacity to perform at a given level. Moreover, the basis for limitations of organ function that leads to limitation of exercise performance are not uniform among patients even at a given stage of the disease. Thus, in early stages of disease, abnormalities in ventricular filling may lead to dyspnea as a limitation to exercise performance while in late stage heart failure, there are limitations to maximal skeletal muscle blood flow which appear to be related to salt in water metabolism rather than to hormonal effects of either angiotensin or enhanced sympathetic activity (22). Similarly, renal blood flow may be limited when the renin angiotensin system is activated and in this circumstance, retention of salt and water may become a limiting factor making the clinical situation worse. With this latter consideration in mind, edema, salt retention, and the need for diuretics at a given level also remains a therapeutic endpoint. All of these factors need to be evaluated relative to time and may help to predict the direction of change in the disease process. With this last consideration in mind, a clear therapeutic endpoint is the need for increased medical intervention. Thus, the need for increased diuretics or vasodilators in the course of disease would appear to indicate a worsening of the process at least relative to the peripheral circulation.

In summary, therapeutic endpoints in the treatment of myocardial failure and congestive heart failure relate to the specific endpoint that one is seeking to change. The major considerations revolve around survival and quality of life.

REFERENCES

1. Factor, S.M. and Sonnenblick, E.H. Prog. in Cardiovas. Dis. 27: 395-420, 1985.
2. Anversa, P., Beghi, C., Kikkawa, Y. and Olivetti, G. Circ. Res. 58: 26-37, 1986.
3. Capasso, J.M., Malhotra, A., Scheuer, J. and Sonnenblick, E.H. Circ. Res. 58: 445-460, 1986.

4. Topol, E.J., Traill, T.A. and Fortuin, N.J. NEJM 312: 277-283, 1985.
5. Kugler, J., Maskin, C., Frishman, W.H., Sonnenblick, E.H. and LeJemtel, T.H. Circ. 66: 1256-1261, 1982.
6. Donald, D.E., Rowlands, D.J., Ferguson, D.A. Circ. Res. 26: 185-199, 1970.
7. Mancini, D.M., LeJemtel, T.H., Factor, S.M. and Sonnenblick, E.H. Am. J. Med. 80: 2-13 (Supp. 2B), 1986.
8. Nelson, G.R., Cohn, P.F. and Gorlin, R. Circ. 52: 408-412, 1975.
9. Califf, R.M. et al. In: Congestive Heart Failure (Eds. E. Braunwald, M.B. Mock and J.T. Watson), Grune & Stratton, NY, 1982, pp. 31-40.
10. Litchfield, R.L., Kerber, R.E., Benger-Martz, A.L., Sepko, J., Bhatmayar, R. and Marcus, M.L. Circ. 66: 129-134, 1978.
11. Hakki, A., Weinreich, D.J., DePace, N.L. and Iskandrian, A.S. J. Cardiac. Rehab. 4: 38-43, 1984.
12. Siegel, L.A., LeJemtel, T.H., Strom, J., Maskin, C., Forman, R., Wexler, J., Ribner, H. and Sonnenblick, E.H. Am. Heart J. 105: 1042-1047, 1983.
13. LeJemtel, T.H. and Sonnenblick, E.H. NEJM 310: 1384-1385, 1984.
14. Massie, B.M., Kramer, B.L. Circ. 69: 1135, 1984.
15. Furberg, C.D., Yusuf, S. and Thorn, T.J. Am. J. Cardiol. 55: 45A-47A, 1985.
16. Cohn, J., Archibald, D.G. and Ziesche, S. NEJM 314: 1547-1552, 1986.
17. Keren, G., Bier, A., Strom, J.A., Laniado, S., Sonnenblick, E.H. and LeJemtel, T.H. Am. Heart J. 112: 517-525, 1986.
18. Lee, W.H. and Packer, M. Circ. 73: 257-267, 1986.
19. Cohn, J.N., Levine, T.B., Olivari, M.T. NEJM 311: 819-823, 1984.
20. Francis, G.S. Cardiovas. Rev. & Reports. 6: 444-454, 1985.
21. Goldman, L., Hashimoto, Cook, F. and Luscalzo, A. Circ. 64: 1227-1233, 1981.
22. LeJemtel, T.H., Maskin, C.S., Lucido, D. and Chadwick, B.J. Circ. 74: 245-251, 1986.

3

Evaluation of Ventricular Function in Patients with Heart Failure: Invasive or Noninvasive?

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Before considering the question as to whether ventricular function should be evaluated invasively or noninvasively in patients with heart failure, it may be useful to review the goals in the treatment of heart failure and the reasons for evaluating ventricular function.

The major goals in the therapy of heart failure are to improve exercise performance; improve quality of life and functional class; and improve survival. While it might seem obvious that one should evaluate ventricular function in a condition such as heart failure in which there is a primary abnormality of cardiac function the situation becomes somewhat less obvious when one examines the relation of ventricular function to the goals in the treatment of heart failure. Several studies have failed to show any significant relationship between resting ventricular function before or after a therapeutic intervention and subsequent exercise performance or functional improvement (1-7). For example, an improvement in left ventricular ejection fraction and cardiac output has been seen after administration of vasodilators without a subsequent long term improvement in exercise tolerance (8). Similarly there is a poor correlation between the effects of a therapeutic agent on left ventricular ejection fraction during exertion and subsequent exercise performance or functional improvement (9). There is little evidence that any hemodynamic parameter including: left ventricular ejection fraction; cardiac output; left ventricular filling pressure; diastolic function, or systemic vascular resistance predicts exercise performance. There has however been a suggestion that a change in right ventricular ejection fraction may be a predictor of a change in exercise performance (10). There has not however been sufficient

experience with therapeutic interventions to be certain of the meaning of any given change in right ventricular function after therapeutic intervention and subsequent exercise performance or functional class.

The failure of an improvement in these indices of ventricular function to predict an improvement in exercise performance suggests that other factors such as peripheral vascular reserve, distribution of cardiac output during exertion and peripheral metabolism may be of greater importance than central hemodynamic factors despite the primary of abnormal cardiac function in the pathogenesis of heart failure. Studies by Zelis et al in edematous patients with heart failure have demonstrated a decrease in peripheral vascular reserve (11-12). Agents that increase exercise performance in edematous patients with heart failure may act by causing a loss of sodium and water from the periphery thereby restoring vasodilator reserve and improving the distribution of cardiac output to working skeletal muscles. The situation in nonedematous patients with compensated heart failure appears to be less clear in that a reduction in peripheral vascular reserve has not been confirmed (13). It is however possible that inadequate pressure development during exercise (13) a metabolic defect impeding oxygen utilization (14) or activation of the renin-angiotensin system during exercise with resultant peripheral vascular constriction (15) may impair exercise performance. The efficacy of converting enzyme inhibitors in compensated heart failure may be linked to this latter mechanism.

The situation in regard to an improvement in survival and a change in resting or exercise hemodynamics is also uncertain. Although there is convincing data suggesting that resting left ventricular ejection fraction is an excellent predictor of survival (16) there is less certainty as to the meaning of a change in left ventricular ejection fraction after therapeutic intervention for subsequent survival. The V-Heft Trial of vasodilator therapy has shown a relationship between an improvement in left ventricular ejection fraction and survival (17). Whether a similar relationship exists for inotropic agents such as digoxin or the newer inotropic agents such as milrinone remains to be determined.

In view of the uncertain relationship between hemodynamic measurements and the effect of therapeutic interventions on the major goals in the treatment of heart failure what is the role of the measurement

of ventricular function either invasively or noninvasively in the evaluation of a new therapeutic agent?

Before embarking upon clinical trials of a new therapeutic agent in patients with heart failure the mechanism of action will have been determined from preclinical studies. It is however essential to verify the mechanism in man. This is usually best accomplished by careful invasive hemodynamic evaluation in a limited number of patients. For example, the phosphodiesterase inhibitors were thought to be positive inotropic agents based upon preclinical evalaution (18). Subsequent clinical studies have suggested that although they have a positive inotropic effect they have a major vasodilator effect (19). Determination of the mechanism of action may be valuable in anticipating the need for subsequent clinical trials and likely drug interactions. One should determine the effect of the therapeutic agent on standard hemodynamic parameters including: heart rate; mean arterial pressure; pulmonary arterial pressure; right and left ventricular filling pressure; ejection fraction; cardiac output; systemic vascular resistance; and some index of inotropic effect for example, determination of the relationship of end systolic volume to end systolic pressure under various pressure loads (20-21). The initial hemodynamic study should also attempt to determine whether the agent is effective in improving cardiac output over a wide range of ventricular function or only in certain subsets for example, those with an elevated left ventricular filling pressure, elevated systemic vascular resistance, or decreased ventricular compliance. The effect of the therapeutic agent on myocardial oxygen consumption is also of importance as is the effect of the agent on the balance between myocardial oxygen demand and supply, as evidenced by changes in regional myocardial wall motion, lactate production or other indices of ischemia. These hemodynamic parameters are best interpreted when they are derived from placebo controlled trials in view of the many factors that can influence hemodynamic status such as: emotional state with catecholamine and neurohormone release, contrast medium, and concurrent therapeutic agents. While it is desirable to perform these hemodynamic measurements both acutely and chronically at rest and during exertion this may not always be feasible in view of the reluctance of many patients to undergo repeat catheterization. In view of the uncertain relationship between either resting and or exercise hemodynamics these

chronic measurements, although of interest may not be essential. It should however be emphasized that the demonstration of an acute hemodynamic effect does not necessarily predict a chronic effect (22). A chronic effect of the agent can be ascertained by demonstrating a persistent improvement in exercise tolerance on serial exercise testing. Some indication that the acutely demonstrated mechanism of action for example; vasodilator, positive inotropic, or change in left ventricular compliance persists over time is desirable and should be obtained noninvasively if it cannot be demonstrated invasively. With certain classes of agents it may be necessary to obtain serial hemodynamic measurements such as end systolic volume or ejection fraction to be reassured that there are no long term adverse effects. The time of the repeat study is arbitrary but probably should be a minimum of 1 month and preferably three months from the acute study.

While a well controlled invasive hemodynamic study is useful to explore the initial mechanism of action and potential adverse effects on the balance between myocardial oxygen demand and supply it should be pointed out that recent advances in noninvasive techniques including radionuclide ventriculography, doppler echocardiography, peripheral digital contrast angiography, fast CT imaging, and nuclear magnetic resonance imaging make it possible to obtain most if not all of the desired information noninvasively. If noninvasive techniques are used for the initial hemodynamic studies careful documentation of the reproducibility and accuracy of the technique should be provided. With current technology it should be possible to determine whether an agent acts as a positive inotropic agent, vasodilator, or affects ventricular compliance using noninvasive techniques. It should also be possible to determine if the agent has any adverse effects on the balance between myocardial oxygen demand and supply, as evidenced by changes in regional myocardial wall motion. It is also possible to measure the distribution of cardiac output at rest or during exertion noninvasively (23).

After the initial studies to confirm or establish mechanism of action and potential adverse hemodynamic effects measurement of ventricular function is of value in selecting patients for inclusion into larger dose finding, efficacy, or safety trials. Measurement of left ventricular ejection

fraction and or diastolic function is useful in the initial selection of patients to establish the presence of a cardiac abnormality as the cause of the patients symptoms of fatigue, dyspnea, or edema. When possible the etiology of the ventricular dysfunction should be established for example, ischemic heart disease, idiopathic dilated cardiomyopathy, hypertensive heart disease, alcoholic cardiomyopathy, etc. Although most studies have lumped ischemic and idiopathic cardiomyopathy together for investigation of therapeutic agents it is possible that a given agent may be useful in one and not another etiology. Hemodynamic characterization of patients to be included in a trial may also be useful if particular subsets have been identified in initial studies of mechanism of action in whom the agent has a beneficial effect, such as those with an elevated left ventricular filling pressure, elevated peripheral vascular resistance or decreased ventricular compliance. Determination of left ventricular ejection fraction also provides information as to subsequent risk of mortality. This characterization, in a relatively large number of patients can be performed noninvasively. There is a good correlation between left ventricular ejection fraction determined invasively and that detected by radionuclide ventriculography, 2D echocardiography, peripheral digital contrast angiography, or cine CT imaging. Recent studies suggest that left ventricular ejection fraction may also be reliably obtained from simple clinical parameters and the chest x-ray (24). Attention should also be directed to determining left ventricular hypertrophy and mass since recent studies have suggested that left ventricular hypertrophy is an important risk factor for cardiovascular death (25).

After hemodynamic characterization of the patient for inclusion into a trial of a therapeutic agent the decision as to whether serial measurements of ventricular function are needed will depend upon the mechanism of the agent tested and the evidence that the investigator or sponsor wishes to accumulate to support a claim for efficacy. As emphasized above, there is relatively little evidence linking an improvement in ventricular function to an improvement in exercise performance or functional class. After the initial hemodynamic characterization efforts should be directed toward proving efficacy, for example by demonstrating an improvement in exercise performance, functional class, or survival. While sequential measurements of ventricular

function may be of only limited value in determining efficacy they may however be of considerable value in assuring that ventricular function has not deteriorated. For example, high dose catecholamine administration might improve cardiac function and exercise performance, but over time cause further cardiac cell necrosis. Withdrawal of the drug after several months might reveal ventricular function to be worse than prior to starting therapy. When evaluating agents with this potential serial measurements of ventricular function such as ventricular volumes and ejection fraction would be indicated both in patients with the therapeutic agent and in control patients on placebo.

In summary, a simple recipe for the study of a new therapeutic agent for heart failure cannot be given in view of the varied etiology, pathophysiology, and potential mechanisms of action. In general however, a well designed placebo controlled invasive hemodynamic study in a relatively small number of patients which defines mechanism of action and characterizes the effect of the agent on cardiac hemodynamics, distribution of cardiac output, renal function, peripheral metabolism and the neurohumeral profile should be part of the initial evaluation of any new agent for use in heart failure. Should one choose to use noninvasive techniques for this initial evaluation care should be taken to provide evidence for the reproducibility and reliability of the measurements and to provide equivalent information to that obtained by invasive study. After this initial characterization larger scale studies should be performed in which noninvasive techniques may be used to define the patient population and assure that there is no deterioration of cardiac function over time. The understanding of the pathophysiology of heart failure and the effect of therapeutic agents on the major therapeutic goals is rapidly expanding. A well designed approach to the study of a therapeutic agent for heart failure will depend upon the unique properties of that agent and the emerging knowledge from both small and large trials evaluating mechanism and clinical end points. Reliance on a formula that worked for the last agent that was approved for clinical use may not suffice as new knowledge and understanding accumulates.

REFERENCES

1. Franciosa, J.A., Park, M. and Levine, T.B. Am. J. Cardiol. 41:33, 1981.
2. Engler, R., Roy, R., Higgins, C.B., McNally, C., Buxton, W.H., Bhargava, V. and Shabetai, R. Am. J. Cardiol. 49:1832, 1982.
3. Goldberg, M.J., Franklin, B.A., Rubenfire, M., Kernin, N.Z., Willens, H.J. and Ruskin, R. J. Am. Coll. Cardiol. 2:887, 1983.
4. Haq, A., Rakowski, H., Baiqrie, R., McLaughlin, P., Burns, R., Tihal, H., Hilton, D. and Feiglin, D. Am. J. Cardiol. 49:439, 1983.
5. Portz, S.J., Kirch, D.L., Groves, B.M., Lindenfeld, J., Leitner, M.N. and Horowitz, L.D. Circulation 74(Supp II):138, 1986.
6. Benge, W., Luchfield, D.O. and Marcus, M.L. Circulation 61:955, 1986.
7. Rubin, S.A., Chattergee, K., Gelberg, H.J., Ports, T.A., Brundage, B.H. and Parmley, W.O. Am. J. Cardiol. 43:810, 1979.
8. Packer, M., Medina, N. and Yushak, M. Am. J. Cardiol. 57:1323, 1986.
9. Szlachcic, J., Massie, B.M., Kramer, B.L., Topic, N. and Tubau, J. Am. J. Cardiol. 55:1037, 1985.
10. Baker, B.J., Wilen, M.M., Boyd, C.M., Dinh, H. and Franciosa, J.A. Am. J. Cardiol. 54:596, 1984.
11. Zelis, R., Longhurst, J., Capone, R.J., et al. Circulation 50:137, 1984.
12. Zelis, R. and Flaim, S. Prog. Cardiovasc. Dis. 24:437, 1982.
13. Wilson, J.R., Wicner, D.H., Fink, L.I. and Ferraro, N. Circulation 74:775, 1986.
14. Rubin, S., Chatterjee, K. and Parmley, W.O. Am. J. Cardiol. 43: 399, 1979.
15. Kirlin, P.C., Grekin, R., Das, S., Ballor, E., Johnson, T.J. and Pitt, B. Am. J. Med. 8:623, 1986.
16. Taylor, G.J., Humphries, J.O., Mellits, E.D., et al. Circulation 62:960, 1980.
17. Archibald, D.G., Cohn, J. and VA Cooperative Study Group. Circulation 74(Supp II):309, 1986.
18. Farah, A.E. and Aloosi, A.A. Life Sci. 22:1139, 1978.
19. Terris, S., Bourdillon, P.D.V., Cheng, D., Latts, J., Olsen, S., Nicklas, J. and Pitt, B. Am. J. Cardiol. 58:596, 1986.
20. Suga, A., Sagawa, K. and Shoukas, A.A. Circ. Res. 32:314, 1973.
21. Grossman, W., Braunwald, E., Mann, T., McLaurin, L.P. and Green, L.H. Circulation 56:845, 1977.
22. Packer, M.J., Meller, J., Medina, N., Yushak, M. and Gorlin, R. N. Engl. J. Med. 306:57, 1982.
23. Strauss, H.W., Harrison, K. and Pitt, B. J. Nucl. Med. 18:1167, 1977.
24. Cease, K.B. and Nicklas, J.M. Am. J. Med. 81:429, 1986.
25. Kannel, W.B. and Abbott, R.D. Am. Heart J. 111:391, 1986.

4

ASSESSMENT OF NEUROHORMONAL PARAMETERS IN CONGESTIVE HEART FAILURE: DETERMINATION OF SODIUM AND WATER REGULATION

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INTRODUCTION

The term "neurohormonal" has arisen as a simplified means to identify the wide array of chemical mediators of central and peripheral nervous system activity, and a diverse group of structurally different hormones, that mediate a variety of homeostatic mechanisms in man. The importance of these neurohormones in congestive heart failure, is not a recent discovery; their contribution to the pathophysiology of heart failure has been studied over several decades yet these substances have been more aggressively evaluated in the last ten years. This is due primarily to two factors: first, the availability of accurate radioimmunoassay and radioenzymatic techniques, and second, the ability to pharmacologically inhibit a variety of these pathways with relatively specific probes. For instance, the use of captopril to specifically inhibit the renin angiotensin system has become the paradyme of these inhibitors, providing not only physiologic information, but also a potent new approach to therapy. A summary of neurohormonal contributions in congestive heart failure would require a step-wise assessment of a well intergrated lattice-work of relationships that is beyond the scope of this presentation. To focus these issues somewhat more clearly, the present report will

highlight the importance of factors that regulate sodium and water excretion in man, and their derangement in patients with congestive heart failure.

ADVERSE EFFECTS OF SODIUM AND WATER RETENTION IN CHF

The etiology of congestive heart failure may vary from patient to patient but inappropriate sodium and water retention is usually a common final pathway in the majority of these patients. Watkins and co-workers demonstrated this in a convincing canine model of congestive heart failure (1). They demonstrated that the renin angiotensin system was activated early in the course of congestive heart failure. However, as aldosterone-mediated sodium and water retention resulted in greater and greater volume expansion, the increased volume load eventually suppressed the renin angiotensin system in a reciprocating fashion. It is clear that inappropriate retention of sodium and water may be one of the primary long-term morbid consequences of congestive heart failure that may have a diverse array of manifestations and effects. The primary hormonal pathway responsible for sodium and water retention, is the renin angiotensin system, where fluid retention can be a manifestation of the vascular effects of angiotensin II, but more directly, fluid retention is a result of excessive secretion of aldosterone, which promotes the reabsorption of sodium and water. In addition, an increase of plasma vasopressin will result in an increase of free water absorption by the kidney. Suppression of alternate hormonal pathways may also result in sodium and water retention. For instance, suppression of the favorable effect of vasodilatory prostaglandins, dopamine, and atrial natriuretic factor may be important for the pathogenesis of sodium and water retention. Once activated, the retention of sodium and water will

result in expansion of both intravascular and extravascular fluids compartments which result in congestion of vascular tissue, and interstitial tissue. This effect is typically manifest by dyspnea and peripheral edema. Ultimately, this will result in a low output state, with progressive cardiac failure due to ventricular overload. Additional target organ changes resulting from volume expansion include hepatic congestion with a reduction of synthetic processing and skeletal muscle congestion. Increased fluid in the interstitial space, and within skeletal muscle, may contribute to the reduction of exercise capacity observed in congestive heart failure.

IMPAIRMENT OF GLOMERULAR FILTRATION RATE IN CHF

The kidney is ultimately responsible for the excretion of sodium and water, and the abnormal sodium retention of congestive heart failure may result not only from hormonally-mediated vascular and functional adjustment within the kidney, but also intrinsic renal impairment. The latter may not be apparent until congestive heart failure has reached a stage of at least moderate impairment. In mild congestive heart failure, where renal blood flow and cardiac output is only slightly decreased, glomerular filtration rate is maintained by an increase of filtration fraction. This reflects adjustments in sympathetic nervous system activity, and enhanced efferent arteriolar tone, which is mediated by an increase of angiotensin II. As cardiac output and renal blood flow are further decreased, there is a further reduction of glomerular filtration rate, as the reflex increase of filtration fraction is no longer sufficient to compensate for the reduction of renal blood flow. This progresses to a stage where there is further reduction of the renal fraction of cardiac output. This situation is

consistent with a primary role for afferent arteriolar tone and blood flow as the primary determinate of glomerular filtration rate. The increase of filtration fraction at this stage is not adequate to protect glomerular filtration rate. While the autoregulatory adjustments that govern this response are in many respects mediated by neurohormonal pathways, glomerular filtration is dependent on the fraction of renal blood flow reaching the kidney in the most severe heart failure.

EFFECTS OF DIURETICS IN CONGESTIVE HEART FAILURE: FAVORABLE AND UNFAVORABLE

Diuretics provide the primary therapeutic means to reduce the intravascular and extravascular fluid excess in heart failure. Diuretics have been the traditional treatment for fluid overload in heart failure patients and they are of particular benefit to patients with acute heart failure, or chronic heart failure associated with marked peripheral edema. The more potent loop diuretics, when used alone or in combination with other agents, block proximal tubular sodium and water reaborption, thereby increasing sodium and water delivery to the distal tubules and collecting ducts.

There are several adverse effects of diuretics that may be more manifest in severe congestive heart failure. First, is the activation of several hormonal pathways by loops diuretics. It is well established that diuretics will activate the renin angiotensin system (2,3), and this effect may be more pronounced in patients with severe heart failure. Second, the sodium depletion induced by diuretics is also associated with an increase of sympathetic nervous system activity. This may be particularly harmful in congestive heart failure where sympathetic nervous activity is already

increased, and this enhanced activity may be associated with greater frequency of morbid events. Diuretics will also increase circulating levels of arginine vasopressin. An additional factor that is not as readily appreciated, is the fact that overall vascular tone becomes much more dependent on circulating levels of angiotensin II in the presence of sodium depletion. In early studies of converting enzyme inhibitors, it was well established that there was a greater tendency for orthostatic hypotension in the sodium depleted state (4). Following the administration of the intravenous converting enzyme inhibitor teprotide, orthostatic hypotension, to the point of fainting, was induced in the majority of normal volunteers. We subsequently studied this phenomenon in congestive heart failure patients, demonstrating a similar effect with long-term converting enzyme inhibition (5). Of interest was the fact that rapid administration of 500 ml of physiologic saline over twenty minutes, was able to reverse the orthostatic hypotension. This did not appear to be the result of volume expansion, as the amount of fluid administered was relatively small. Therefore, it was postulated that this effect was due to reducing the dependence of vascular tone on the renin angiotensin system. Diuretics may also have an adverse effect on renal function, perhaps mediated by the degree to which hormonal pathways are activated. Whether this is a factor of altered glomerular driving pressure, or a direct effect on the renal tubules, requires additional studies. An additional factor which is likely to result from the adverse interplay of diuretics and hormonal pathways is the metabolic derangement observed in congestive heart failure patients. Hypokalemia due to an increase of tubular potassium wasting, occurs as a result of excess secretion of aldosterone. Hyponatremia has received

considerable attention in the literature, as a marker of renin system activity, and as a prognostic factor in congestive heart failure. There are no studies to date that demonstrate marked hyponatremia except in the presence of diuretic therapy. For instance, in a recent sodium balance study in patients with moderate to severe heart failure (6), we did not observe hyponatremia, as both dietary sodium, and free water intake were carefully controlled. In the diuretic treated population, such rigid controls are difficult to achieve. Patients are subjected to large doses of diuretics, often in combination which promote sodium excretion together with an increase in thirst, that results in an increase of free water intake. When coupled with the effects of diuretics on renin, aldosterone and vasopressin secretion, that dilutional hyponatremia is observed. These adverse effects of diuretics have remained somewhat obscured in the literature of congestive heart failure, where all patients are maintained on digoxin and diuretic therapy.

SODIUM BALANCE STUDIES IN CONGESTIVE HEART FAILURE.

In an attempt to better define the contribution of hormonal pathways to sodium and water retention in heart failure, in the absence of the comfounding influence of diuretics, we studied a group of patients with moderate to severe congestive heart failure using metabolic sodium balance techniques (6). In this study, we monitored sodium and water excretion during sodium depletion (10 mEq) and sodium repletion (100 mEq). Diuretic therapy and vasodilators had been discontinued in these patients. In the absence of diuretic therapy, the metabolic abnormalities that are typical of the diuretic treated patient, such as hyponatremia, were not observed. We observed small

but significant changes in left ventricular filling pressure, but overall vasoconstriction and impairment of cardiac output was present for both sodium intakes, and intravascular volume was not altered. However, dietary differences were manifest by a two kilogram weight increase on the 100 mEq sodium diet. Most important was the effect of dietary sodium on the renin angiotensin system and sodium excretion. During the 10 mEq sodium diet, which in may respects is analagous to diuretic therapy, there were significantly greater levels of plasma renin and aldosterone. During the 100 mEq sodium intake however, plasma renin and aldosterone were not only normalized, but were actually suppressed below normal, in a number of the patients. Not all individuals handled the 100 mEq sodium diet in the same way. Half of the patients were able to excrete the 100 mEq sodium load, and it was in this group that the renin angiotensin system showed the greatest suppression. The remainder of the patients, however, continued to avidly retain sodium and water, and it is in this group that the renin angiotensin system remained activated. This study provided convincing evidence that the macula densa signal for renin release in heart failure remained exquisitely sensitive despite the severity of heart failure. That is, the renin secretory response was readily regulated by the amount of sodium that was delivered to the distal tubule. We further observed that the hemodynamic response to converting enzyme inhibition with captopril was dependent on the state of sodium balance. During the 10 mEq sodium intake, where vascular tone was maintained by the renin angiotensin system, a favorable reverse of vasoconstriction was observed. However, during the 100 mEq sodium intake where the renin angiotensin system was suppressed, there was little if any hemodynamic response to captopril. For

the first time, this study demonstrated that within a given group of heart failure patients, the response to converting enzyme inhibition could be mediated by changes in dietary sodium intake, by altering the extent to which vascular tone was dependent on angiotensin II. This may, in part, explain the somewhat phasic response to converting enzyme inhibition that is often observed in heart failure patients. Thus, this study provides a clue to why some patients do not initially respond to captopril, but then show a favorable long-term response when diuretics dosages are upwardly adjusted. Alternately, these observations help explain the phenomenon which most clinicians have observed with captopril. Namely, when captopril is initiated in the hospital where dietary sodium and diuretics are well managed, a favorable response to captopril is observed. However, during long-term follow up where dietary sodium intake is poorly managed, fluid retention and a blunting of the favorable hemodynamic response may occur. In this study we were unable to identify what hemodynamic or hormonal factor was responsible for the avid sodium and water retention in half of our patients during the 100 mEq sodium diet. This observation led us to consider the potential pathophysiologic role of atrial natriuretic factor in congestive heart failure.

REGULATION OF SODIUM AND WATER EXCRETION BY ATRIAL NATRIURETIC FACTOR

It is well established that atrial myocytes secrete one or more peptides, collectively known as atrial natriuretic factor, whose active peptide fragment results in an increase of sodium and water excretion (7). We recently evaluated endogenous levels of ANF, and the hemodynamic, hormonal, and renal responses to exogenous infusion of ANF, in both normal

subjects and patients with congestive heart failure (8). In our subjects, and reports from other groups (9,10), there is a significant increase of the circulating form of immunoreactive ANF in congestive heart failure patients, ranging anywhere from three to five fold, when compared to normal subjects. It had been postulated early in the evaluation of ANF that congestive heart failure patients might have a reduction of circulating levels of ANF thereby accounting for sodium and water retention. However, the increase of circulating levels suggesting that the amount of ANF produced in heart failure should be sufficient to induce natriuresis and diuresis. An alternative explanation was that while circulating levels were increased, the target organ responsiveness to ANF was decreased. This indeed appears to be the case. While a direct vasodilating effect can be demonstrated with ANF administration in heart failure, that in many ways are similar to that of normal subjects (11), there is a blunting of the renal responsiveness to ANF administration. The magnitude of sodium and water excretion does not approach that of normal subjects and may possibly be explained by a shift of the dose response curve, due to the chronic increase of ANF levels in heart failure. Administration of atrial natriuretic factor also produces suppression of the renin angiotensin system in normal subjects. This effect would be logical, as a reciprocating relationship mediated by the extent of atrial distention. In heart failure, the renin suppressing effect is blunted compared to normals while a blunting of aldosterone secretion, is consistent with the independent effect of ANF on aldosterone secretion that was reported in animal studies. The blunting of the renin response to ANF, despite increased circulating levels of the endogenous hormonone,

suggests that abnormalities of ANF responsiveness may contribute to the adverse sodium and water retention in congestive heart failure.

WHAT SHOULD BE THE FOCUS OF THE ASSESSMENT OF NEUROHORMONAL FACTORS IN CONGESTIVE HEART FAILURE?

There is a sufficiently large body of data identifying the importance of abnormal neurohormonal mechanisms in the regulation of vascular tone and sodium and water excretion. However, the importance of these pathways can only be ascertained when studies are designed prospectively to directly assess the effect of these hormones and their interactions. Casual measurement of these hormones particularly in uncontrolled clinical trials may result in a large body of misinformation that will prevent or obscure a precise definition of their contribution to the pathophysiology of congestive heart failure. Therefore, it would not seem appropriate to measure circulating levels of these hormones in a random fashion, for every new drug under development. As the physiologic effects of these hormonal pathways are generally well defined (at least in normal subjects), sufficient information is available to correctly construct prospective studies that evaluate the influence of drug therapy on these hormonal pathways, and more importantly, the target organ effects that these hormones induce. Therefore, it is difficult to speak with certainty on the importance of a given level on aldosterone, for instance, without a good estimation of sodium and water intake, and output, at the time that the reference level of the hormone is measured.

Important information can be obtained from clinical studies, as exemplified by the numerous studies of converting enzyme inhibition in congestive heart failure, which represent for the most part,

studies performed with captopril. The importance of these clinical studies, in terms of sodium and water regulation, rest with the fact that the most important effect of converting enzyme inhibitors may be the long term reduction of aldosterone, thereby facilitating sodium and water excretion. The effects of converting enzyme inhibitors on vascular tone are less cleanly defined, and at times are paradoxical. In the setting of diuretics where vascular tone is more dependent on angiotensin II, converting enzyme inhibitors are likely to induce the most favorable hemodynamic effects; namely, reduction of arterial afterload and perhaps even improvement of venous capacitance. However, it is in this group of individuals that provocation of hypotension is most likely to occur. The significant degree to which blood pressure is reduced can be masked if only supine blood pressure is monitored. Many individuals who are able to compensate in this supine position have marked orthostatic hypotension in the upright position (5,6). Such severe hypotension can induce a variety of hemodynamic and target organic embarrassment nonetheleast of which is inducing further progression of renal impairment (12,13). First, glomerular filtration rate, which is mediated by an angiotensin II dependent increase of filtration fraction, can be reduced by converting enzyme inhibition. This would likely be acceptable, if the degree of total renal blood flow, or afferent arteriolar flow was increased in response to a total reduction of afterload. However, if renal perfusion pressure is decreased, at the same time that efferent arteriolar tone is decreased, net glomerular filtration pressure can be radically reduced, so that further reduction of glomerular filtration rate will occur.

For physiologic studies of sodium and water regulation, different criteria must be applied.

Whether the clinical trials are sponsored by federal agencies or the pharmaceutical industry, several factors must be taken into consideration. It should be realized, that there is little if any information which identifies the progression of abnormal sodium and water retention, related to activation of neurohormonal pathways. The time course of activation of these hormonal pathways, as well as phasic alteration of activation remain to be clarified. Second, studies that are designed to address mechanisms of sodium and water regulation in heart failure must be performed in the absence of other drugs. Ideally, this includes discontinuation of digoxin therapy which may have a direct supppressant effect on some hormonal pathways such as the renin angiotensin system. More importantly, it would be mandatory to perform studies in the absence of diuretic therapy, which can adversely effect any interpretation of the data acquired, because of the confounding effects outline above. There is a growing tendency to consider captopril as the third drug in the standard treatment regimen of heart failure. While this is eminently reasonable from a clinical point of view, it should be recognized that it would be difficult to interprete the mechanisms governing sodium and water excretion in the presence of captopril therapy, unless the response to captopril was the specific endpoint desired, in comparison to baseline data. Optimally, to understand the importance of neurohoromonal regulation of sodium and water excretion, it would also be necessary to consider the interaction of a given hormone with other hormonal pathways, such as the relationship of atrial natriuretic factor to renin release. It would also be important to consider the response of hormonal pathways to alterations in dietary sodium intake.

REFERENCES

1. Watkins, L.,Jr., Burton, J.A., Haber, E., Cant, J.R., Smith, F.W. and Barger, A.C. J. Clin. Invest. 57:1606-1617, 1976.
2. Ikram, H., Chan, W., Espiner, E.A. and Nicholls, M.G. Clin. Sci. Mol. Med. 59:443-449, 1980.
3. Francis, G.S., Siegel, R.N., Goldsmith, S.R., Olivari, M.T., Levine, T.B., Cohn, J.N. Ann. Int. Med. 103:1-6, 1985.
4. Sancho, J., Re, R., Burton, J.A., Barger, A.C. and Haber, E. Circulation 53:400-405, 1976.
5. Cody, R.J., Franklin, K.W., Kluger, J., Laragh, J.H. Circulation 66:135-141, 1982.
6. Cody, R.J., Covit, A.B., Schaer, G.L., Laragh, J.H., Sealey, J.E., Feldschuh, J. J. Clin. Invest. 77:1441-1452, 1986.
7. deBold, A.J., Borenstein, H.B., Veress, A.T., Sonnenberg, H. Life. Sci. 28:89-94, 1981.
8. Cody, R.J., Atlas, S.A., Laragh, J.H., Kubo, S.H., Covit, A.B., Ryman, K.S., Shaknovich, A., Pondolfino, K., Clark, M., Camargo, M.J.F., Scarborough, R.M., Lewicki, J.A. J. Clin. Invest. 78:1362-1374, 1986.
9. Tikkanen, I., Fyhrquist, R., Metsarinne, K. and Leidenius, R. Lancet ii:66-69, 1985.
10. Bates, E.R., Shenker, Y. and Grekin R.J. Circulation. 73:1155-1161, 1986.
11. Cody, R.J., Kubo, S.H., Atlas, S.A., Laragh, J.H., Ryman, K.S., Shaknovich, A. Clin. Res. 34:476A, 1986.
12. Powers, E.R., Bannerman, K.S., Stone, J., Reison, D.S., Escala, E.L., Kalischer, A., Weiss, M.B., Sciacca, R.R., Cannon, P.J. Am. Heart J. 104:1203-1210, 1982.
13. Packer, M., Lee, W.H., Kessler, P.D. Circulation. 74:766-774, 1986.

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THE ASSESSMENT OF QUALITY OF LIFE AND EXERCISE RESPONSE IN PATIENTS WITH CHRONIC CARDIAC FAILURE

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The symptom complex of chronic congestive heart failure is primarily composed of generalized fatigue and dyspnea, resulting in a limitation of exercise capability. In addition to the extensive morbidity associated with the disease, there is a growing appreciation of the excessive mortality that occurs in a population of patients with symptomatic heart failure. Thus, 2 fundamental goals of therapy for the patient with congestive heart failure are to improve the quality of life and to extend survival. Although measuring the impact of a therapy on mortality involves the evaluation of large numbers of patients followed for long periods of time, the endpoint of death is simple, unambiguous and without controversy. The same can not be said of the assessment of changes in quality of life. The purpose of this report will be to review the problems associated with our current efforts to objectively quantitate the effect of therapy on the signs, symptoms, exercise tolerance and general well-being of the patient with chronic cardiac failure.

An assessment of quality of life must encompass a number of different measurements. For example, in a recent study on the

effects of antihypertensive therapy on the quality of life, Croog et al. (1) examined: 1) the sense of well-being and satisfaction with life, 2) the physical state, including a review of physical symptoms and a scale of sleep dysfunction. In this category also, was an analysis of sexual function; 3) the emotional state, 4) intellective or cognitive functioning, tested by such devises as the Wechsler memory scale and the Reitan trial making test and 5) the ability of the patient to perform in social roles and the degree of satisfaction derived from these roles. This area included measurements of work performance social participation in and outside the family and perceptions of the future. A number of fairly standard scales and indexes were used in this analysis, and interviews were carried out on all patients at least 4 times during the trial. Quantitative scores were derived for each test and were used in a statistical comparison of the change in quality of life as a result of different antihypertensive therapies.

This excellent study is used as an example of the time, effort and thought that is necessary before any rational, objective assessment of quality of life can be performed. It also serves as a focus to discuss the increased complexity of such an assessment in patients with heart failure. In the antihypertensive study, the authors sought to investigate a homogeneous population. Thus, only white men, aged 21 to 65 years, who were fully employed and had no significant disease process other than uncomplicated essential hypertension were entered. This population contrasts markedly to the typical group of patients with chronic heart failure, who are from diverse social and economic backgrounds, usually on disability, and

who have a variety of other medical problems including arrhythmias, diabetes mellitus, angina pectoris, peripheral vascular disease and depression. More important, the study population in the hypertension trial was initially without symptoms and on no concomitant medications other than the study medications. Obviously, this is a distinct difference from the usual heart failure patient referred to a tertiary care center for an investigational trial. These patients have a multiplicity of symptoms despite the administration of a number of different medications.

Furthermore, the results of the quality of life interviews in the referenced study could be correlated to the precise measurement of the systemic blood pressure, as well as the specific side effects associated with the study medications. The major difficulty with the clinical syndrome of congestive heart failure is that it is a dynamic and poorly understood process. There are no obvious markers for the severity of heart failure or the rate of progression of the underlying myocardial dysfunction. For a given patient with chronic cardiac failure, there is a poor correlation between symptoms, exercise tolerance, left ventricular function and prognosis (2,3). Thus, we have no "gold standard" against which we can compare any change detected by a battery of quality of life interviews. Moreover, because of the complexities of their medical problems and pharmacologic regimens, it becomes very difficult to ascribe cause and effect to any single drug intervention.

There are other, more general problems associated with the assessment of quality of life, which have been thoughtfully and extensively reviewed by others (4,5). Some of these difficulties are

particularly vexatious when studying a population of all patients with congestive heart failure. 1. Role of personal effort and external support. The New York Heart Association functional classification grades the severity of heart failure on the amount of physical work that can be accomplished without symptoms. What this and many other functional classifications fail to consider is the effort expended in performing a given task. Patients with heart failure often compensate for their disease by avoiding stairs, walking more slowly or taking early retirement. As a result, a casual review of their symptoms may reveal that they have very few complaints of breathlessness or unusual fatigue because they fail to exert themselves to an activity level which will elicit the symptoms. Likewise, attempts to take a sexual history from a male patient can often be thwarted by such responses as "my wife is not interested in sex" or "I'm widowed." Employment status and job satisfaction are greatly influenced by the level of education and amount of physical work required during the working day. A management consultant may continue working despite rather severe symptoms of heart failure, while a postman or manual laborer usually needs to seek disability early in the course of his disease. Thus, any index that grades the ability of a patient to perform a task needs to incorporate a scale of effort expended to accomplish the task. This is the rationale behind the development of the Borg scale of perceived exertion (6).

2. Role of personal preferences. As physicians, our ability to judge a patient's progress is prejudiced by our own perceptions of disability. A diuretic may be prescribed for a patient with paroxysmal nocturnal dyspnea complaining of sleeplessness. The

following week, his physician may mark the patient's status as improved because he no longer has nocturnal dyspnea but the patient acknowledges no improvement because he continues to be awakened at night to urinate! Some patients are extremely discomforted by orthostatic dizziness with the angiotensin-converting enzyme inhibitors, while others accept the side effect in exchange for the relief of other symptoms. Obviously, any index of disability must determine which difficulty is most important to the patient. 3. Lack of validity testing of most questionnaires to chronic heart failure patients. Most of the indexes available to grade changes in quality of life or disability have not been formally tested for their ability to serve that function in patients with heart failure. This may be because of the many problems discussed above and because a measurement of change in the physical status of these patients is not easily discernable. However, it can not be assumed that a previously validated index will be appropriate to apply to the study of heart failure. Deyo and collegues (7,8) have demonstrated that the Sickness Impact Profile worked well in identifying post-therapeutic changes for patients with acute low-back pain, but not for patients with rheumatoid arthritis. The example discussed by Feinstein et al. is even more applicable to our current dilemma (5). He cited an unpublished study that examined the effect of a pharmacologic therapy on cardiovascular symptoms. The investigators had used the Sickness Impact Profile during the course of the study to assess quality of life changes. However, when they were questioned more closely, they agreed that their belief was that an improved quality of life was the relief of certain cardiac symptoms. However, cardiovascular symptoms

are not included in the variables assessed by the Sickness Impact Profile!

With the advent of intensified research into the pathophysiologic abnormalities that occur in heart failure, more precise, accurate and objective measurements of improvement in symptoms were needed, particularly as a method of assessing the effects of therapeutic interventions. Given the many problems associated with the development of a standardized quality of life index, cardiologists naturally turned to a familiar method of assessing a patients' ability to exert themselves, the graded exercise test. Maximal exercise tolerance, measured with either a treadmill or bicycle and quantified as total exercise duration or total work done, has quickly proven to be a reliable index of functional status in patients with chronic cardiac failure. However, a number of controversies currently surround our heavy reliance on the maximal exercise test as a measure of efficacy in investigational drug trials.

The results obtained with stress testing are markedly dependent on the motivation of the subject and the experience of the supervising physician. Several reports have emphasized the need to perform serial tests to insure the reproducibility of a baseline exercise tolerance, because patients frequently improve with successive exercise tests. One solution to this problem is to perform concomitant respiratory gas exchange during each test. In this way, maximal oxygen uptake, VO2 max, can be measured, and it can be determined if, in fact, the patient made a maximum effort during exercise. Various investigator have either used the attainment of

anaerobic threshold or an increase of the respiratory exchange ratio (9) to indicate that maximal effort was expended. Indeed, Weber et al. (3) have shown that the measurement of VO2 max in patients with chronic heart failure is the most objective estimate of cardiac reserve. It has thus become the routine of some laboratories to correlate an improvement of VO2 max after a drug intervention with an augmentation of cardiac performance. Unfortunately, the reverse has also been assumed to be true ie. if no increase in VO2 max occurs, then the patient has not benefited from the drug.

A growing body of evidence suggests that this negative corollary may not be completely true. Normally, VO2 max is not limited by pulmonary function or the metabolic capacity of skeletal muscle to maximally extract oxygen (10,11). Therefore, as long as subjects exercise with at least 50% of their total muscle mass, the major limitation to VO2 max in healthy persons is maximum cardiac output (12). In patients with congestive heart failure, improvements of peak exercise hemodynamics after therapy have not always been translated into an acute augmentation of VO2 max (13-15). In addition, Mancini and co-workers (16) reported on the results of chronic captopril therapy in patients with severe heart failure. They observed that peak VO2 increased only when there was a concomitant rise in peak skeletal-muscle blood flow after therapy. The fundamental concept that unifies these observations is that VO2 max is limited not only by cardiac output but by the delivery of oxygenated blood to the exercising muscles.

A second problem with the use of maximal oxygen uptake as an important measure of drug efficacy is that many patients with heart

failure cannot attain a true VO2 max. Instead, exercise is usually terminated because of symptoms of fatigue and breathlessness, and peak VO2 is used if the respiratory exchange ratio exceeded 1.0. The difference between peak VO2 and VO2 max can range from 1-3 ml/kg/min (12) and, therefore, introduces a range of uncertainty of 5-25% in the measurement. This range can be one source of error in the serial exercise testing performed in a drug trial, and may account for the improvement of VO2 seen in patients on placebo. Nevertheless, Kappler et al. (17) have recently demonstrated remarkable reproducibility between 2 exercise tests done 2 weeks apart in 47 patients with heart failure. Maximal systolic blood pressure, peak VO2 and exercise duration were all highly reproducible between the 2 tests for the group as a whole, but they did note individual patients with poor reproducibility between measured variables.

An additional problem occurs when both exercise duration and oxygen consumption are used as endpoints in a trial. We have recently reported on a comparison of the 2 measurements in 85 patients treated with an angiotensin-converting enzyme inhibitor, 1 of 2 phosphodiesterase inhibitors or placebo for an average of 8 weeks (18). In all treatment groups, the magnitude of change in exercise duration greatly exceeded the change in VO2 max. Moreover, exercise duration did not always change in parallel with the response in VO2 max. A critical issue in the design of future interventional trials will be to determine the most desirable effect we can hope of a drug for heart failure. Is a drug more efficacious if it improves both peak VO2 and total exercise duration or is it enough merely to improve symptom-limited exercise? This dilemma will be compounded as

we utilize still other endpoints into routine exercise testing, such as measurement of the anaerobic threshold.

Probably the most important critique of our heavy reliance upon maximal exercise testing in heart failure trials is that patients do not routinely expect to exert themselves maximally in the course of their daily living. In fact, most clinicians would agree that a more reasonable goal for these patients is to allow submaximal exercise to be carried out in greater comfort. Thus, a standardized form of submaximal exercise testing is clearly desirable. Many investigators are currently evaluating different forms of submaximal exercise tests.

Finally, even as we use the objective parameters of exercise testing, we must avoid making assumptions about the applicability of the results obtained to common clinical situations. A recent study highlights the unexpected results that can occur when several different methods are used to assess the effects of therapy. Cowley et al. (19) followed 10 patients with moderate heart failure who still had symptoms despite 40 mg furosemide daily. They were all randomized to either increased doses of furosemide or captopril and subsequently crossed over to the other form of therapy. Four different methods were used to measure the response of exercise to therapy: 1) a symptom-limited maximal exercise test, 2) the Borg perceived exertion score was recorded at each submaximal stage of exercise, 3) a self-paced corridor walk test of 100 meters at 3 speeds: slow, normal and fast--determined by the patient and 4) a visual analogue score of symptoms of dyspnea, fatigue and general well-being. Both treatments improved symptom-limited exercise

tolerance but furosemide had a more favorable effect. Perceived exertion during submaximal exercise was reduced by similar amounts with both treatments. The time taken to walk 100 m at a self-selected slow speed was reduced with both drugs, again furosemide had a more beneficial effect. Furosemide had a more favorable effect on visual analogue scores for dyspnea, fatigue and general well-being.

This study illustrates that an expanded view of measurements of exercise performance may be able to detect important but subtle differences in therapy that are overlooked when only maximal exercise testing is used. A concerted effort must be made to develop forms of submaximal exercise testing that can be broadly applied. Furthermore, renewed efforts should be made towards the development of a sensible, applicable questionnaire concerning quality of life changes in the patient with heart failure. Only then will we be ready to truly test the efficacy of drug therapy.

REFERENCES

1. Croog, S.H., Levine, S., Testa, M.S., Brown, B., Bulpitt, C.J., Jenkins, C.D., Klerman, G.L., Williams, G.H. N. Engl. J. Med. 314: 1657-1664, 1986.
2. Franciosa, J.A. Am. J. Cardiol. 53: 1447-1450, 1984.
3. Weber, K.T., Kinasewitz, G.T., Janicki, J.S. Circulation 65: 1213-1223, 1982.
4. Wenger, N.K., Mattson, M.E., Furberg, C.D., Elinson J. Assessment of quality of life in clinical trials of cardiovascular therapies. LeJacq., New York, 1984.
5. Feinstein, A.R., Josephy, B.R., Wells, C.K. Annal. Int. Med. 105: 413-420, 1986.
6. Borg, G. Scand. J. Rehab. Med. 2: 92-98, 1970.
7. Deyo, R.A., Diehl, A.K. Spine 8: 635-42, 1983.
8. Deyo, R.A., Invi, T.S. Health Serv. Res. 19: 277-89, 1984.
9. Ribeiro, J.P., Hartley, L.H., Colucci, W.S. Heart Failure 1: 102-111, 1985.
10. Johnson, R.L., Jr. Circ. Res. 20: 154-160, 1967.
11. Gollnick, P.D., Armstrong, R.B., Saubert, C.W. J. Appl. Physiol. 33: 312-319, 1972.
12. LeJemtel, T.H., Mancini, D., Gumbardo, D., Chadwick, B. Heart Failure 1: 112-124, 1985.

13. Maskin C.S., Forman, R., Sonnenblick, E.H., LeJentel, T.H. Am. J. Cardiol. 51: 177-182, 1983.
14. Franciosa, J., Cohn, J.N. Circulation 59: 1085-1091, 1979.
15. Kugler, J., Maskin, C.S., Frishman, W.H., Sonnenblick, E.H., LeJemtel, T.H. Circulation 66: 1256-1261, 1982.
16. Mancini, D., Davis, D., Wexter, J.P., LeJemtel, T.H. Circulation 70: 193, 1984 (abst).
17. Kappler, J., Ziesche, S., Nelson, J., Francis, G.S. Heart Failure 2: 157-163, 1986.
18. Likoff, M.J., Hare, T., Gumbardo, D., Chadwick, B. Heart Failure 2: 164-175, 1986.
19. Cowley, A.J., Wynne, R.D., Stainer, K., Rowley, J.M., Hampton, J.R. Lancet 2: 770-772, 1986.

DISCUSSION -1

Dr. Morganroth: The incidence of heart failure appears from Dr. Yusuf's data to be doubling every fifteen years. Was this incidence population adjusted or were the data in per thousand?

Dr. Yusuf: There are at least three discernible reasons why those numbers are increasing. One, is as Joel pointed out an increase in the population. The second reason is that the population is growing older and heart failure is more a disease of the older people. Both of these do not fully explain the increase and once you control for that, both for the number of people and have a common denominator like 100,000 people and once you control for age distributions, both the incidence of deaths due to heart failure has still doubled in the last two decades.

Dr. Swedberg: A key factor in the progression of myocardial failure is sympathetic activity. It was mentioned, but I don't think it was emphasized enough and I would like to hear the panel discuss the importance of sympathetic activity in relation to the deleterious effect on the myocardium.

Dr. Cody: I think it is an important role, like some of the other hormonal pathways. It is not clear as far as I understand, when the sympathetic nervous system is activated and how it progresses and frankly, why it progresses. Certainly after an acute infarct or early in the course of failure, you can understand why it would occur, but why the adaptation is there chronically, I don't understand. Everybody is demonstrating increased circulating levels of norepinephrine and epinephrine. They probably are associated with a detrimental effect; whether they cause a detrimental effect or whether this is a reflection of the extent of the underlying abnormality I don't think is clear.

Dr. Cohn: As we know the relationship between the activity of the sympathetic nervous system as assessed by plasma norepinephrine and survival has been established at least in our and in some other laboratories now, so there does seem to be a relationship between the activity of the sympathetic nervous system and a shortened life expectancy. The mechanism of the relationship is really unclear. We don't know what cause and effect is because there is clear evidence that the sympathetic nervous system becomes activated when left ventricular function is abnormal and relates probably to the symptoms of heart failure. What we don't know is whether this is just a marker for the severity of the heart disease and the severity of the circulatory abnormality or whether it is a pathophysiologic mechanism in the progression of the syndrome. If it is a pathophysiologic mechanism is it mediated via an adverse effect on the myocardium? There are many potential mechanisms by which the sympathetic nervous system could aggravate the myocardial cell directly or is it mediated through an adverse effect on the systemic circulation via changes in compliance and resistance in the vascular bed and progressive changes in pre-load and impedance which therefore progressively impaired ventricular performance? If it is the former, one would like to block the role of the sympathetic system on the heart and thus the beta blocker mechanism which the Swedish group has explored. If

one wants to interfere with the sympathetic and periphery, one uses drugs which interfere with either alpha 1 or alpha 2 receptors or some vasoconstrictor or vasodilator effect. These approaches are secondary approaches. One can inhibit the sympathetic nervous system more proximally by inhibiting it centrally or by reducing nerve traffic. The sympathetic nervous system normalizes beautifully after transplant, so I think we are still in the descriptive phase of the role the sympathetic nervous system is playing. The sudden death problem is a real one of course and half of everybody's patients are dying suddenly in the face of stable ventricular function and stable exercise tolerance and it is such an attractive hypothesis that the sympathetic activation is playing a role in sudden death. We really don't have evidence to confirm that it is indeed the patient with the highest sympathetic tone who is dying suddenly.

Dr. Sonnenblick: There is a subset problem. When a fellow has heart failure related to an acute myocardial infarction he has lost half his heart. Then the catecholamines perhaps play a role. It may be quite different in somebody with cardiomyopathey where the primary reason that his heart is in trouble could be due to the catecholamines or catecholamines interacting with abnormalities that have been induced perhaps even by viruses affecting the cell surface membrane so that it isn't just a generic problem of the arrhythmias at the end affecting the catecholamine responses in the middle but the subset of what was the primary disease so that it really requires some very basic research. I think catecholamines are important but it may be a very different problem in the beginning than at the end of the disease.

Dr. Packer: I think that maximal exercise performance and the limitations of that is extremely important. We have tried to use a lot of the tests which have been proposed in the literature to look at maximal oxygen consumption in a patient population which I would presume more resembles a class IV than class II and III. It is really very hard to use these tests in patients who are symptomatic. In a very advanced patient population the difficulty is in reproducibility with tremendous intra-day variation. The maximal peak varies from day to day. Many also are anaerobic at rest, so anaerobic threshold is very hard to identify and you can't get enough points if they only exercise for three or four minutes to actually identify an anaerobic threshold if you define it as a change in the slope of the line. Have you, Dr. Jessup had any experience in patients who are very ill in terms of maximal exercise performance and is there a mechanism of judging efficacy using exercise testing in this kind of patient population?

Dr. Jessup: I think your points are well taken. I think that the respiratory gas parameters help us to insure that the patient is exercising maximally or to the best of their ability. Certainly there is a group of patients who are very ill called Class E patients that are producing lactate at rest. It really is unrealistic to try to do a maximal exercise test on them. What we have tried to do in looking at those kinds of patients is actually developing submaximal exercise tests. For instance, the corridor walk test has turned out to be sort of a nice thing to do in

patients, to just time how long it takes them to walk a certain distance. These patients also seem to do a little bit better on a bicycle rather than on a treadmill, which would be not what I would have predicted, but for some reason, I guess they are supporting more of their weight and they do better on bicycles. We have also had some experience, at actually measuring lactate changes during submaximal exercise which might be applicable to the very sick patient that is producing lactate at rest. I totally agree that it is much more difficult in very ill patients. I don't think however we should abandon trying to do any form of exercise testing in this group of patients because our other parameters are just as difficult. I think hemodynamics are so bad, ejection fractions are so bad, we need to look at different ways of assessing exercise response.

Dr. Packer: I wouldn't suggest abandoning them. All of the measures that we have are so imperfect that the more information, the more parameters, the more slices of the pie that we can get, maybe we will learn something. I think the ultimate question in all of these tests is, what are we trying to measure? What is the core of heart failure? Is heart failure a disease which is characterized by LV dysfunction, by exercise intolerance, by hormonal disequilibrium? If we knew what heart failure was, then we would be able to measure it and if we don't know what it is then all of these are successive approximations of an unknown truth and that is the biggest problem.

Dr. Morganroth: Let me interject a question for both of you. One has to be practical from a study design point of view to answer a simple question whether a new drug will have an impact in the patient group which we are calling "congestive heart failure" or not. We don't want to design a trial in which we have 50 different potential end point measures which involve various types of exercise, VO_2 measurements, etc. Which exercise parameters would you measure. Would you do VO_2's as part of a multi-center trial? What type of exercise would you suggest be used.

Dr. Jessup: I think that there is enough evidence to suggest that exercise testing really requires concomitant respiratory gas exchange. I think there needs to be a form of submaximal exercise testing which I have tried to say is up for grabs as for the most appropriate way. Those are the two components of exercise testing. Now there are a number of different ways you can approach submaximal exercise testing, but I would still say.. by the way I do want to interject. I think when you design trials, we have to just say we cannot test the hypothesis in patients that have resting lactate levels above normal or are that severe. I mean we are dealing with an end state population that it is not fair to test drugs in that group of patients.

Dr. Packer: I have a concern in applying respiratory gas exchange to 20 centers in a multi-center trial. Can all 20 centers do it with equal facility? It is probably better than having all 20 centers all do exercise duration which is more subject to reproducibility problems. I think that the patient population depends on the drug and it depends I think more than anything on the expertise of the investigators. That is a factor which I don't

think has been really sufficiently appreciated by most of the people who have participated in multi-center trials and their experience is a big factor in how the trial comes out.

Dr. Morganroth: So you are not recommending VO_2's for a CHF trial endpoint?

Dr. Packer: I am not recommending VO_2s as a sort of cure all but neither is Dr. Jessup. I think that there is a problem with all of these tests. To directly address the question, if you have 6 parameters of efficacy and we don't know which one is the best parameter, the more evidence that you have that a drug changes these parameters, the more critical mass of data that you have that the drug works in the treatment of heart failure.

Dr. Lipicky: Before leaving that topic, let's say that one does look at exercise tolerance and at oxygen uptake and that somehow or another the oxygen uptake measured in sequential exercises doesn't perform up to expectations or you would say something is wrong. Now what do you do? Do you drop that patient? You no longer pay attention to that patient. Indeed the patient's maximum exercise tolerance is increased but VO_2 hasn't changed or in fact has gone down and you are confronted with having to make choices because you have two measurements. Is there an idea about how to treat that.

Dr. Jessup: I agree. I think that is a very difficult problem, and maybe it is simplistic of me to think this, but I would suggest that we at the beginning of a trial, say these are two separate variables that we are going to look at just as if you know usually in heart failure trials it is rare to see an improvement in the ejection fraction. It doesn't stop us from measuring it and wanting to know what happens to CT ratios or whatever. I would say we are going to look at two variables of exercise tolerance. One is total exercise duration and one is VO_2max. You don't have to throw out a test if the machine breaks (which happens to us) or if for some reason, the patient coughs or giggles during a test, you don't have to throw out the entire test. You can include the VO_2 data. You can include the exercise test duration and look at it as two separate parameters.

Dr. Lipicky: There was a second part to the same question. I mean that sounds fine to me, but if indeed there is uncertainty with respect to what exercise tolerance test to use from the vantage point of what functional thing does this represent, why measure it at all?

Dr. Jessup: I think then we get to the point, and I don't want to steal from Milton's thunder, but my own feeling is that is why we need to do placebo controlled trials. If we look at exercise duration, I mean, certainly Captopril was approved on the basis of exercise duration improvement alone and I think most of us agree it has been an extraordinarily useful drug. If we could do that study over again, with VO_2 max, maybe VO_2 would improve, maybe it wouldn't. It doesn't take away from the fact that exercise duration is improved. So what I am saying to answer your question is, I think that if exercise duration is improved more significantly than placebo, then that is a desirable end point, one

desirable end point of a drug. If it improves VO_2 max, that may be measuring two separate issues.

Dr. Lipicky: Let me just rephrase the question. The implication is that response to exercise somehow or another is inexorably tied to an evaluation of congestive heart failure. Why do you think that is true? Is that really so?

Dr. Jessup: I think it is only a corner of what is happening in heart failure. I think that is exactly what Dr. Sonnenblick was trying to say in the beginning of his remarks that exercise intolerance is certainly one marker of the severity of heart failure. To say we have cured heart failure with exercise improvement has done nothing for underlying progression of the disease. We have done nothing for mortality or for the arrhythmias. I am saying we haven't cured heart failure by improving exercise tolerance.

Dr. Sonnenblick: I think Mariell went onto where I would get to. That is just one component and you have to decide what is the problem of that multifactorial system that one is trying to impinge on for the patient. There is a certain dilemma that Dr. Lipicky faces and regulatory agencies face, for example, if the patient complains of a headache and you relieve the headache, what was the reason for taking the pill if it didn't hurt him. Do you then need to have some other quantitative measurement, except his headache got better? The same thing in heart failure; if the fellow is a little less short of breath, is that adequate to say a drug is useful even though it doesn't do anything transcendental to the disease? It is kind of nice. It is perfectly possible that giving him heroin on a regular basis would also make him feel better, do more, and make him feel happy and in a fatal disease perhaps it is the best drug. I mean we do that in cancer, but I am not sure we don't do it with a drug with the same life course as cancer. If you are solving a symptom, why not just settle for the symptom change? When we don't have any evidence what we have changed the disease and we don't even know what the disease is a large part of the time, we are formalizing ignorance as if formalizing it will make it sound better and sell better and perhaps it will. But the bottom line is Captopril got approved because people felt better. We then found an argument to support its use.

Dr. Morganroth: Dr. Lipicky do you agree with him.

Dr. Lipicky: If I were to make the assertion that exercise capacity is truly inexorably linked to heart failure, and that the model that I carry around is that basically heart failure is somehow an inability of demand to be met by supply and that exercise in general, whether it be Class IV congestive heart failure or mild to moderate congestive heart failure, that exercise impact usually makes it worse and lack of exercise usually makes it better and in that sense, the capacity to exercise is really kind of a functional measure of the state of the whole circulation. Would there be disagreement with that and that in fact exercise tolerance is one of the most important measures.

Dr. Sonnenblick: What we showed is exactly that the model is wrong. When the model is wrong we have to go back to first concerns. I know of no data that says that the model is correct and everytime it has been tested it has been shown to be wrong. There

is no good correlation between what the heart is doing and your exercise capacity. That is a bombshell to me. I wish it were otherwise. It would be pretty to think so, it just isn't the case. I mean if the ejection fraction has no good correlation with exercise performance it means that there is something wrong with the model. If you want to make the patient feel better, that isn't the model and I have no problem with that. Where we get into trouble is where we assume that the model is O.K. We started out measuring exercise performance in most studies 5-6 years ago. As we found the ejection fraction did not improve or get better in more and more studies. It has been dropped because it is an embarrassment. It doesn't look good if you have to show that the ejection fraction went down and then your patient died, you would rather say, gee, well look at the exercise. I think the fact of the matter is, the ejection fraction doesn't go the way you might like in the studies and therefore the way to do it is say, "We'll if we want to get this approved, don't measure ejection fraction, just measure exercise performance and maybe we can sneak under the wire."

Dr. Temple: I am almost embarrassed. I have a question about something that came up earlier, not these global more interesting questions.

Dr. Morganroth: Do you want to hold then for a second and we will finish this topic? Is the idea of doing exercise tolerance and always including measures of oxygen utilization directed at making exercise tolerance better by, for example, excluding patients who don't seem to be able to achieve maximum oxygen utilization, which I would say would be reducing beta error kind of maneuver, or is it designed to be sure that you don't reach the wrong conclusion because some other effect that you hadn't anticipated might give you the wrong answer? In other words, is it trying to remove a potential.. eliminate the possibility of a wrong positive finding or is it to reduce beta error? The importance of that obviously is a company might choose to avoid reducing beta error because it is too expensive to do it and take its own risks, whereas, if you would reach a wrong conclusion, we would be interested in that. We worry about alpha error, and they worry about beta error in a sort of quick way. Is that question clear?

Dr. Sonnenblick: In my view it is both. In addition, though you can fine tune that. For example, that is where the submaximum comes in. If you are measuring oxygen consumption you can ramp that, if you can look at a lactate level at steady state relative to VO_2, you have a quantitative interrelation between the two which you just can't do with time. So I think it is the beta error that comes in. I think you really need both if you really want to get the answer.

Dr. Temple: What you are saying is that if you don't do oxygen utilization, you may have put people into an exercise tolerance setting that they shouldn't be in because they are not likely to show improvement because that is not their problem. O.K. so the patient doesn't improve, if there are not too many of those you can still have a study that works out and as Milton was

saying, doing this in 26 different centers may not be worth it. Could you get wrong favorable answers? Let's conclude there was an improvement in exercise tolerance when in fact something else happened other than really improve.

Dr. Sonnenblick: Absolutely. Actually you can get two minutes error just in the noise and most of the studies have sold on two minutes.

Dr. Temple: Yes, but error doesn't produce findings. Error produces noise and eliminates findings. Is there some way that you could reach wrongfully the conclusion that exercise tolerance was improved when in fact something else happened that caused that to happen?

Dr. Sonnenblick: Yes, I think you can. There are some arguments that a large part of the capital improvement was not related to exercise performance in reality, but more what Mariell was talking about. Not VO_2 related but related to how well you felt and how well you could do.

Dr. Lipicky: The answer to that question depends on the model that you carry in your head. Your response to my question was that exercise tolerance doesn't necessarily reflect whether or not the heart got better and could reflect something other than the heart getting better. The question then is if indeed you can't conclude from that measure that the heart got better, but people can exercise longer, does that mean that this is not a therapy for congestive heart failure. If exercise tolerance gets longer, can you be wrong? You might not be able to draw conclusions about the heart but would it be a wrong conclusion with respect to the treatment of the entity.

Dr. Sonnenblick: I think that is exactly the point. If you are worried about exercise, you have studied exercise, but don't imply that it is the heart that you have cured. I agree with you entirely. I think the misconception is that if you exercise longer, it meant the heart got better. I agree with you entirely. I think the model that says exercise is exercise, the heart is the heart, is probably a more direct model.

Dr. Temple: So you should do oxygen measurements if you want to understand things and it is not as clear if you have to do it if you just want to get your drug through.

Dr. Sonnenblick: If you said it, it is probably the bottom line.

Dr. Yusuf: Dr. Sonnenblick burst one bubble. I mean, exercise is not related to how well the heart performs. It is another reason why we are doing exercise because we think it is an objective measure of functional capacity. I mean, this is what we all hear. I mean is it objective if we get a number and we know that number in heart failure has as big as a 25% error. I know of two studies that have actually looked at that question and the correlation between VO_2 a maximal exercise capacity with day to day exercise activities is absolutely 0. We really don't know what it means. It is a physiological endpoint, but it doesn't correlate with what people do day-to-day and we really need that thing before we use that as an end point. The second part of it is, there is some data to suggest that certain types of submaximal exercise which are

related to the way people perform in their day-to-day activity. For example the six minute walk test is very crude but somehow that correlates much better with day-to-day activity than these artificial things you do on a treadmill. So we really have to stand back from it and think, what does it really mean? Sure, you could say that maxVO_2 got better. But does it end there, or does it really mean the patient got better in some way? I think we have to ask that question. The third thing I wanted to comment on, was the plea to measure a lot of things and then something will come out. I mean, first, if one thing got better and something else got worse, you would focus on what you wanted to focus on. That is one thing, but the second thing is, an analytical nightmare. When you have many of these things, you know when you toss a coin in a number of times, you are going to get something happening by chance, so even in the well designed placebo controlled trial, if you measure twenty different things, one or two are definitely going to be statistically significant even if you actually gave placebo with placebo. I would urge some restraint on the multiplicity and sort of use some ideophysiological sense or common sense or statistical sense in deciding how many of these multiple end points you are going to look at.

Dr. Cohn: Let me see if I can make some sense out of this morass of exercise issues in heart failure. The syndrome of heart failure is indeed a syndrome of reduced exercise tolerance. In fact, that is how we recognize the patient, and make the diagnosis. It is reduced exercise tolerance in the setting of ventricular dysfunction. It is not a mystery why we use exercise tolerance to evaluate the patient. That indeed is the diagnostic criterion for making the diagnosis of heart failure. We have heard this morning several people who have suggested that exercise tolerance has nothing to do with the prognosis of heart failure. Unfortunately that is not true. It is true, I completely agree that ventricular dysfunction and exercise intolerance are very poorly correlated unless you include normals. If you include normals in your correlation, then of course they are correlated, because normals have normal ventricular function and normal exercise tolerance and people with heart failure, have reduced ventricular function and reduced exercise tolerance. They are related, but they are very poorly correlated with a very low r. They do represent quite distinct pathophysiologic abnormalities in the setting of the syndrome of heart failure. When you look carefully at prognostic factors, exercise tolerance is an independent prognostic factor for survival, independent of ejection fraction. So if you have a patient with an ejection fraction of 30%, the lower his exercise tolerance, the shorter he is going to live. So, it does become an important factor in the severity of the syndrome. Both the low ejection fraction and the low exercise tolerance are independent factors in predicting survival. Now the problem with testing exercise is that we tend to use it as a surrogate for quality of life and symptoms. I mean that is the simple way in the laboratory that we can test what somebody can do and we think that will have something to do with how sick they are. The discouragement has been as Dr. Jessup has pointed out and everybody else has

pointed out that it doesn't really work that way. It isn't quite so simple. The severity of exercise disability doesn't correlate very well with how sick people feel they are. Would an improvement of exercise tolerance correlate with an improvement of quality of life? We don't know that very well nor do we yet know whether an improvement of exercise tolerance will correlate with an improvement in survival. So there are too many holes yet in this whole sequential thing to answer the question. Now how valuable are oxygen consumption measurements during exercise? We have committed ourselves to VO_2 measurements in anaerobic threshold measurements in VHEFT because we have been convinced over a number of years that at least in many laboratories the ability to distinguish a real physiologic end point for an exercise test is nil. People's motivation creates a lot of effect on how long your work on a treadmill or bicycle ergometer, and therefore you need some objective measurement. The fascinating thing about VHEFT data is, and this is unpublished, when you look at VO_2 as a predictor of mortality, it is very good in heart failure. If you tease out those patients who achieved and surpassed an anaerobic threshold, and everybody who exercises maximally surpasses an anaerobic threshold, the problem isn't in getting there, the problem is in identifying it. It is not that people don't get anaerobic when they exercise, it is just that in some people, it is hard to find that point and define it. When you use the criteria that the patient has exercised enough to become anaerobic and look at the relationship between VO_2 and survival, it is very tight, it is very good. When you look at VO_2 motivationally before they reach their anaerobic level, there is no correlation between VO_2 and survival. The gas exchange measurements improve the sensitivity of your method to pick up a true physiologic reduction of exercise capacity which indeed does correlate with life expectancy and yet we still don't know whether that is going to help us a lot in looking at therapeutic interventions. I think Ray Lipicky's concern that one may go one direction and one may go the other is a real one because exercise performance is an integrated response which relates both to the heart which has to be abnormal in part, to the motivation of the patient, to his degree of conditioning to its ability to redistribute flow to exercise and skeletal muscle to the activation of the neurohumoral mechanisms when you exercise and the severity of that and how that alters distribution of flow and oxygen extraction. So you are looking at a whole host of factors when you do an exercise test, and some of those that influence the time on the treadmill, for instance the mechanical efficiency with which people learn to walk on a treadmill or bicycle ergometer will influence the relationship between time of exercise and O_2 consumption. So we do have a very complex system with exercise and it is very hard to tease out any one factor and we are going to see instances where these two measurements, duration of exercise and O_2 consumption and then the third, quality of life assessment are all going to go in different directions and I pity the poor pharmaceutical company that gets a wonderful study and finds things going in all different directions and doesn't know which one to choose. They know which one to choose, but they

are hoping that somebody won't see the data that went in the wrong direction and we don't yet know enough about that integrated response to be absolutely certain which are the measurements we should make and which we should throw out and that is going to be the mission in the next few years is to try to sort that out so that you don't have to make measurements of everything. You can select those measurements which have turned out to be most useful in assessing therapeutic efficacy.

Dr. Morganroth: That which you don't see, you don't have to worry about, therefore, a common decision about how to design clinical trials is to measure one parameter, which has generally been exercise duration. That is why I was sort of interested to get onto this issue about VO_2, submax, exercise. etc from a regulatory point of view. Let's try to find out as much information as we can and then think about what it might mean; this is the proper scientific approach. I guess the question to Dr. Lipicky from a regulatory viewpoint is would you let a pharmaceutical company get away with only measuring exercise duration as a way to be approvable or do you want to see more science by looking at as many parameters as possible in these trials?

Dr. Lipicky: I think that given the state of the art that one ought to measure everything one can and attempt to learn in the process of doing the trials what it is that in fact has predictive value because it is in the drug development process that in fact these things are going to be worked out. I don't see them being worked out in other processes or in other kinds of settings, so my encouragement would be to measure everything one can measure. That clearly raises problems because indeed if you have measured everything that you can measure, some things are going to change just as a function of chance and that indeed raises a major analytical problem but indeed it seems to me that one of the jobs that would be nice to do over the course of the next couple of days is to figure out what kinds of functions really ought to be paid attention to and what kinds of functions one might expect to correlate one with the other, because certainly one of at least our approaches in the past have been that the entire data base must make sense. That is, even if one had declared VO_2 as my principal variable and that came out with a p of .001 twice and nothing else in the data base makes sense, I would argue that that drug didn't work, even though it met all of these tests of an appropriately designed clinical trial. It met its declared prospective objectives and it just didn't hang and all of the other stuff just didn't quite make sense, I would say this just isn't useful.

Dr. Morganroth: What if you don't measure all that other stuff and you only have exercise duration? Could you say that it is not approvable because we haven't looked at the other possible potentials?

Dr. Lipicky: We would use some other reason for saying it is not approvable.

Dr. Packer: I think the points that Dr. Lipicky just raised are extremely important. The whole thing has to make sense. The data has to hang together. You can't just look at one isolated

variable and say that reaches statistical significance. You don't have anything else to show for it. It gets to the whole problem again of what is heart failure. Heart failure is not just exercise intolerance. It is exercise intolerance secondary to left ventricular dysfunction. My view is to show that the drug works in heart failure, you have to show that the drug improves LV function and improves exercise intolerance. You have to show the drug improves LV function and improves exercise intolerance. They don't necessarily have to go parry paseu. If you had a drug that improves exercise intolerance in heart failure, but did not change hemodynamics one iota, would that be an approvable drug for heart failure, and my bias is it would not be an approvable drug.

Dr. Cohn: Are you talking about resting hemodynamics?

Dr. Packer: Resting hemodynamics or exercise hemodynamics.

Dr. Cohn: I mean separate those, because heavens, resting hemodynamics have nothing to do necessarily with exercise intolerance and maybe not anything with the syndrome of heart failure.

Dr. Packer: It definitely has to do with the syndrome of heart failure because it relates to LV dysfunction, they are not correlated. Changes in one are not correlated with changes in the other, but presumably you have to show that if a drug works in heart failure, it could make sense. It also has to improve LV function by some parameter.

Dr. Sonnenblick: One dilemma that you have there is for example, if you take furosemide, it improves exercise performance. I know of nothing to show improved LV performance. It lowers the filling pressure; it lowers the output to move down a given Starling curve. It does nothing to left ventricular performance per se.

Dr. Packer: I think it is not true that diuretics or the aldosterone inhibitors in patients who have marked LV dilatation have that much of a down slope. You know they are on the flat portion of the Starling curve. Most of the studies looking at diuretic intervention long term show a decrease in filling pressure at the same cardiac output. I would consider that to be an improvement in LV performance and therefore, I don't see an inconsistency.

Dr. Morganroth: Is a drug that has no effect on exercise or rest hemodynamics yet has a clear effect on exercise duration approvable?

Dr. Lipicky: I agree with half a hand.

Dr. Cohn: The question Joel, it is not possible to have a real profound effect on exercise tolerance without altering hemodynamics.

Dr. Lipicky: I am not sure that is so. That is not the reason that you don't want to answer that question.

Dr. Cohn: That makes the question really a non-question. If you are really increasing exercise performance, which means you are increasing the skeletal muscle function, you are delivering more blood and oxygen to exercise in the skeletal muscle.

Dr. Lipicky: But what if you found a drug that in fact was magically able to divert all of the cardiac output through skeletal

muscle and took it away from the viscera and the brain and everything else, and still the organism could survive. I should imagine that that would increase exercise tolerance, given the same cardiac output. Granted that is a sort of non-realistic circumstance but it could make a 10% difference in exercise tolerance that would have p of .001 if you had a large enough sample size.
Dr. Cohn: One of the defects in heart failure is that you do not get reflex vasoconstriction in non-exercising vascular beds and if you had a drug which could magically restore constriction to the non-exercising skeletal muscle and divert flow to exercising skeletal muscle, which would be a re-distribution of blood flow and therefore the patient could exercise more and feel better. If all the other parameters were stable, I think that drug would be approvable.
Dr. Lipicky: Indeed I think what one would probably say, I don't know, it would be an interesting one to wrestle with. It might not be a drug for treatment of congestive heart failure. It might be a drug for increasing exercise in people who have heart failure or some other kind of thing. If one found a drug like that it would be a very interesting drug to think ones way through.
Dr. Fisher: What do the drugs do? It disturbs me very much to hear all the talk about exercise in that no one can show that exercise relates to quality of life, or the amount of number of tasks, the amount of effort expended in daily life. If it doesn't prolong life, if it has no discernible effect from the patient's point of view, then it seems to me much more of a scientific gain than a clinical gain and I would suggest that it is of dubious value to license such drugs on that basis alone. The Cardio-renal Advisory Committee of which I am currently a member has expressed themselves on record with regard to antiarrhythmic drugs. There is not a lot to be said about cosmetic reduction of arrhythmia in asymptomatic or minimally symptomatic people if you can't then show that it goes on to have some effect clinically. We all know that most people will give the drugs I am convinced since they think they are prolonging life. One thing that strikes me very strongly is there has to be more of a link between the hemodynamic and physiologic sorts of things you are talking about and the actual benefit to the patient before a drug should be licensed. It is hard to counter an approval if you have a drug that you can show improved survival or secondarily, quality of life. In the angina studies, the FDA and the Cardio-Renal Advisory Committee have accepted exercise testing. The feeling being there is that there is a very strong link between exercise duration and anti-anginal activity. I think this intermediate stuff really has to be filled in before you can convince a lay person who has trouble following a lot of the argument that the drug is a great benefit. The second point I wanted to mention the analytical morass or difficulties of multiple end points. It is not really that much of a problem and that difficult if you can specify a priority on your end points and order your hypotheses a priori and they are down in writing and in print. Here is a study we intend to do and here is our primary end point. I would suggest that if you had defined a change in VO_2 which I am not very enthusiastic about having heard this morning's discussion, but if it were agreed that that

was an adequate end point because it related importantly to the patients quality of life for example, it would be enough to have the two studies with a p=.001 even if you couldn't explain why I am not opposed to black magic if it can be reproducibly documented say in a nice double blind fashion. Then it seems to me that we can benefit the patient population while we worry more about how to clear out all of the underlying difficulties in the science. Dr. Cody: There are certain assumptions here. If everybody agreed that heart failure is a multifaceted disease I don't think there is one drug that can address all facets. I don't think you can expect a drug that improves skeletal blood flow necessarily to prevent sodium and water retention. I think the fact that a drug only addresses one facet but addresses it well, doesn't mean it can't be approved. So that if a drug does improve exercise performance and the ability of the patient to walk upstairs, go down to the corner and shop, that maybe doesn't alleviate the edema, I still think you have a drug there that does something that is very important. Another thing that is a problem with looking at exercise criteria, that as soon as we know everything that controls exercise, it also assumes that what we know about exercise from sports training clinics, from the NASA programs etc. applies to heart failure and we don't know that. I think that the centers that do exercise studies in heart failure several of which are represented here have only been doing that for maybe a decade at most and I think the explosion of that data has still only been in the last three to four years. I don't think we understand that. You could take some very practical mundane issues in heart failure that could affect exercise performance. You are starting with deconditioned individuals. For the most part, patients with 4+ failure for instance you can't exercise at all, basically lay in bed, and all the baroreceptor responsiveness is being totally blunted. Abelman showed that in the late 1960's. So just laying in bed and not doing the simple day-to-day routine deconditions you. These patients are cachectic, they don't have muscle mass. Even if you can get them to exercise, you are going to have a training effect and that is the importance of placebo controls. I think fortunately for they were able to show that even though there was a placebo effect, the Captopril effect was better so that helped them get approved. Unfortunately for Sterling-Winthrop, they showed a placebo effect, but they could not show that the Amrinone effect was better than the placebo effect. Even very practical issues about what kind of exercise, treadmill is appealing because you are walking with a low level of exercise and that is what most people do. Bicycle is different. It requires quadricep and hamstring development which these patients don't have so maybe from that point of view that is not practical exercise, no more than having them swim laps would be an appropriate exercise because they don't have deltoid and trapezoid development. You have to look at the limitations of what you have and then try to work with those. The final point, the maximal O_2, well maybe it doesn't increase, or maybe it is the distribution and that is the relationship of the heart and the periphery that Jay touched on. It might not show an increase of O_2 but if the

O_2 that you have is where you need it, at that point of time, that might be very important.

Dr. Sonnenblick: Actually between Dr. Cohn and Dr. Cody, I mean they have really said very well and if we take just the distribution problem, you can show a patient who is de-trained, re-train him for the same cardiac output re-directing his blood flow to where the organ is namely getting better skeletal muscle blood flow, nothing changing centrally and he is improved and that is part of what Jay was talking about. The placebo affect is not really placebo, it is training and these patients are untrained. You train them and you can show that it has been shown with the beta blockers, and shown everytime it has been looked at. You can get tremendous improvement in skeletal muscle blood flow and performance all by peripheral training effect and redistribution of a given cardiac output to a more useful base for the patient. The other thing is for a limited cardiac output, when you lose that capacity to re-distribute your blood flow, you can go into severe congestive heart failure and die of renal failure of elevating BUN, nothing centrally changing, the only thing you have lost is the capacity to redistribute your blood flow in terms of the organs that you need to function. Patients with very limited cardiac output may not be able to urinate, eat, and walk at the same time, but if they do one of those three, they may be able to do it very well if they are trained to do it with the same bad central cardiac pump but with the capacity to redistribute blood. I think that is great what Jay is saying and what Dr. Cody is saying. This has been our experience, not just off the top of our head, but there is data to support that kind of view. So yes, if a drug improves what the periphery does, it is going to benefit the patient.

Dr. Yusuf: What are we trying to accomplish? I think we have to step back and ask ourselves that. If what we are trying to accomplish is either make the patient feel better or make him live longer, then I think 90% of the conversation that we have had is totally irrelevant. If you have a patient whose ventricular function improves, but nothing else improves; you know, he dies the next day, and he is as asymptomatic as ever, would you approve a drug for that? Or if you have a patient who improves his exercise tolerance, but nothing else improves, and his quality of life is terrible, would you approve a drug for that. Look at the reverse of that, ejection fraction and exercise tolerance don't change at all, but his quality of life in good placebo controlled trials has improved. He feels better and in his day-to-day life he does more. Is that indication for approval of a drug? Isn't it useful that patients do feel better. Perhaps you have a drug that doesn't do a thing for all these three things, but it improves survival. Would you approve that drug or not. Really, I think we need to stand back and say what are the end points that matter to the patient, not only what the end points are.

Dr. Morganroth: Which of those end points in your opinion is of more value and which if any, are mandatory for approval?

Dr. Temple: I will comment on that, but first I have a question. That is, can normal people eat, walk and urinate at the same time and if they can should they?

Dr. Morganroth: We will take that as a rhetorical question.
Dr. Temple: I had one or two accumulated comments, one on the idea of measuring everything. I agree with what other people have said and am not as worried about it as Salim. When you don't quite know how things are working and what makes them work, it does seem prudent to measure a whole lot of things. What one will look for is consistency. I mean, measuring a lot of things and picking the winner is a problem if you have one trial or if you are playing a little game, but as long as you have the most critical endpoints in mind, I don't think it is a danger to measure a whole lot of things. Obviously one doesn't say, O.K. this measurement improved and everything else went awry and that is O.K. so I think as long as one is prudent about interpreting the mass of data, I don't think that is a problem here. You want to achieve something that you are pretty sure is meaningful to the patient and I think improved survival in the absence of anything else is obviously meaningful unless life is so miserable that you ask whether it is worth it. So you have to weigh those two things, but a benign drug that increased survival, even if you had no idea how it did it is fairly obviously a benefit. First of all I just want to remind everybody that there is a quality of life scale that has been used all along. What is wrong with it is that it is too crude and insensitive, but the New York Heart Association classification with all its faults, if it shows improvement, seems to be showing something reasonably meaningful. Describing the change of the state of existence would be meaningful. The trouble with it is the sort of Lazarus effect. It seems to me that there is a tendency to overemphasize understanding what is going on, and I think understanding is very nice. I don't think it is necessary and I don't think it is possible to understand how they fit together logically. If people improve on reasonable measurements, that is if they complain of less dypsnea, less of the symptoms that bring them to the doctor, is this a reasonable measure of exercise performance? I gather that is open to some debate. Any one of those things endpoints strike me as perfectly good reasons to give a drug a claim. Now how you word it, whether as Ray said you say, this improves exercise tolerance in people with heart failure because you don't know if it has anything to do with the heart, I think that is a nicety that doesn't matter that much. Basically one can conclude a drug is useful if it makes a meaningful change in one or more important symptoms. I guess I want to drop back in one respect. You probably don't want to give a sedative that makes people more indifferent to their misery a claim in heart failure. That seems going one step too far, but as long as it is not something really bogus like that, I think any and all of those, if you are pretty sure they are meaningful to the persons complaints is perfectly valid.
Dr. Jessup: I just wanted to make a few practical points. One is that it is not that patients improve their VO_2 max. I mean usually those patients who have showed an improved exercise tolerance and improved VO_2, generally feel very well. What actually happens much more often and particularly with some of the new inotrope agents is that they may not improve their vO_2 max

and yet they feel a lot better and I think that is where most of us are saying that it is not that exercise tolerance doesn't correlate with day-to-day living, it is just that some day-to-day living things clearly improve where exercise tolerance doesn't. The second point that Dr. Packer brought up that I would really like to dispel is that measuring VO_2 max is not that difficult. Just like anything else you have to learn to do it correctly, and with the machinery that we have today it is all done by computer. A few simple trials and you really know how to do that, so I don't think that we can continue to say we can't do VO_2 max at all sorts of centers because it is impossible to be done. I disagree with that.

Dr. Packer: I think it is a matter of experience and training like everything else in the world. There is one thing that Mariell mentioned that I think is worth maybe dispelling as well and that is the inadvisability of entering class IV patients into trials. The question of these are patients which are harder to evaluate in terms of exercise tolerance, they are patients uniquely suited for physiological studies because the rationale for doing invasive measurements is greater in these patients than in class II patients but I think most importantly, you have a safety issue. If you develop a drug, and prove that it is safe in people with class II and early class III heart failure, you have not shown anything about its safety in class III and class IV heart failure and most of the drugs that we use are more dangerous in patients with class III and class IV heart failure and they have the unique side effects in that severe patient population and will inevitably be used first in those patients when it is released on the market. I think from a safety issue primarily and an efficacy issue almost equally as strong that patients with class IV heart failure have to be evaluated in clinical trials.

Dr. Jessup: What I said is they shouldn't be evaluated in exercise trials

Dr. Packer: No problem.

Dr. Yusuf: Sometimes silence can speak louder than noise and when Joel asked the question how many people know the answer to whether VO_2 max is related to functional capacity, some of us were impetuous enough to think we knew the answer but many of you were wiser and kept quiet. Perhaps that indicates what we really need to know before we continue to use that as an end point, is really to evaluate that and find out that it really does correlate with day-to-day activities well or not and if that answer is yes, then perhaps there is a good reason to continue to use it in studies, because after all it is an objective number. If the answer is no or maybe, then we really have to reevaluate our entire strategy about using that particular end point.

Dr. Cohn: It helps to know the delta though. Not the baseline, it is the delta that is really important because we do have a fair amount of data on exercise VO_2 versus sickness

impact profile for instance and assessment of quality of life. A correlation at baseline is obviously very poor there.

Dr. Sonnenblick: I would like to come back to something, it is very easy to forget about the pathology. Early on in heart failure with mild systolic dysfunction, one of the biggest areas of problem is diastolic dysfunction of the heart. These patients may first show up with ankle swelling, a little dyspnea, but not a real problem of peripheral blood flow distribution. Their exercise problem is because they get short of breath centrally. That is your hypertensive elderly individual. That is not what we are talking about here. These patients may actually do better on a calcium blocker and a diuretic without anything else. Yet they are all on digitalis. Cut their digitalis, they improve actually. So that defining a fundamental disease underneath really becomes important. These patients don't have an exercise limitation because of peripheral blood flow. They dilate their periphery normally, it has been shown, there is lots of data for that. Their limitation is they get short of breath centrally. It is a totally different physiological problem. How are they going to respond to drugs is really quite different, yet if we do a VO_2 you are going to get a different total answer and a different mechanism as related to drug. As the disease progresses then the heart becomes the limitation to their cardiac output, then they have a problem of peripheral blood flow limitation locally, it is a different process. If you are still using the VO_2 to study the disease. In a sense, I hate to be argumentative but one feels like Alice in Wonderland. If we were pre-antibiotics talking about treating fever and somebody says I have aspirin and says does aspirin bring down the temperature, that may be nice and I think aspirin should have been approved, but that may not have much to do with what the whole process is about. I do think one needs to know mechanism, if one goes on blindly without mechanism despite good approval techniques, I think the problem is nobody has any illusion right now that we have done anything to affect mortality. I think it is an Alice in Wonderland to say we are going to approve another drug, yet the whole fundamental thing is we still have exactly the same mortality and nobody has anything that impacts on it. I think mechanism really becomes fundamental. The temptation is to continue to give drugs without knowing mechanism and without that kind of an impact, it is all going to be short term palliation.

Dr. Cohn: How can Dr. Sonnenblick sit next to me and say that we have no intervention that affects mortality?

Dr. Sonnenblick: In an important manner.

Dr. Cohn: You establish your own importance then.

Dr. Temple: What Ed is saying sounds to me like the statement that if you can't do everything you want to do, you shouldn't do anything. That doesn't make any sense to me. You don't have to affect mortality by your treatment of angina to want to treat angina, and as far as we know our treatments of angina, most of them, don't affect mortality, one might. If you can improve the symptoms of a person with congestive heart failure in a meaningful way, even if you haven't improved his mortality, I don't see why

one would toss that. One would try to understand how to do better of course and continue to seek new interventions, but it doesn't seem to me, one abandons the other. Also, it seems to me that if you can define what you want in terms of improvement very well, if you can define those measures, you can set up standards that will work whatever the mechanism is. It seems to me that in the past the idea of just how nitroglycerin worked went through multiple evolutions. Really that probably didn't matter that much, what was really needed was good exercise testing and when it became possible to do good exercise testing, then it was possible to show these things. Whatever the mechanism might turn out to be. It is obviously true that if you don't understand mechanism, you may put the wrong people into your study which is sort of what you said before and in that case you will have an unfortunate loss. The beta error will go up and you will make a mistake. I am not saying that is scientifically good, but if you don't exactly know what all the mechanisms are, you can still try to proceed by saying what it is you want to accomplish and seeing if you do so. I mean obviously, the more you know, the better you can do all that. It doesn't require that, I don't think, which is what I heard you saying. That seems overstated.

Dr. Sonnenblick: I think there is a middle point to that, but the problem that concerns me is more and more that the focus is away from finding out the fundamental mechanisms because the temptation is really to design a specific drug and I see that as a sign of the times and it is unfortunate. The basic fund of research underneath it, is becoming less, the applied pharmacology is becoming more. There is a problem when you dissociate the two. At some point you end up just designing drugs without knowing the pathophysiology. I am talking about in the larger generic sense, I don't disagree that you have to do the practical steps and treat the disease as you have it, it is not getting the other part that I find a problem.

Dr. Temple: The counter to that, that seems equally important, is that carrying out rigorous trials to test all the things that you learned in laboratory, sometimes provides a better check on the truth of what you have learned than one's ability to reason about it. I mean how can one disagree with the need to look at fundamental mechanisms, no one would, but I don't think it is all to the bad that sometimes, practical people like drug companies and regulators sort of cut through all that and say well what can I show here. I think it makes a nice mix of trying to get the mechanism and a bottom line attitude.

Dr. Morganroth: On that middle ground, we will have to stop now.

II. PRECLINICAL ISSUES AND PROARRHYTHMIA DEFINITIONS

6

ANIMAL MODELS OF HEART FAILURE

STEWART J. EHRREICH, Ph.D.

1. INTRODUCTION

The complex series of hemodynamic events which leads to heart failure in humans presents a challenge for the industrial pharmacologist who is looking for an appropriate animal model for the disease. In the various clinical conditions called heart failure, reflex mechanisms are triggered by the body in an attempt to maintain hemeostasis in the face of a failing circulation. This further complicates the picture as sympathetic, renin-angiotensin, and other hormonal and neural mechanisms are called into play.

In the case of severe heart failure there is a loss of functioning myocardial cells, which are probably lost at even early stages, making it only possible to partially restore the cardiovascular system towards normal function. Because of this irreparable damage it seems futile to search for a pharmacologic "cure." Recent discussions on the subject by no less than some of the foremost experts on myocardial function, Dr. Lionel Opie and Dr. Pouleur, have resulted in a more pessimistic outlook than ever before (1),(2). Nevertheless, success with vasodilator and other supportive therapy has lead many investigators to believe that such

therapeutic measures provide subjective improvement for the patient, if nothing else, and even if the patient is destined to expire in a relatively short time, the quality of his life will be improved.

While the industrial medicinal chemist and pharmacologist can never reasonably hope to find a compound capable of regenerating lost cardiac muscle fibers they may still search for something to improve the hemodynamic state so that more normal renal and salt/water metabolic functions may be restored.

The present paper will present a review of the literature of the last ten years emphasizing the latest laboratory approaches to heart failure, as well as the presumed mechanism for the heart failure. Whatever the approach, it will be quite obvious that no one model is close enough to the clinical condition to be called the exact replica, forcing the scientist to accept what appears to be the most reliable primary screening and secondary evaluation models.

Several review articles on the subject of animal models for heart failure have been published in the last ten years. The paper by Smith (3) cites literature beginning about 15 years prior to its publication. The review by Evans discusses the various models currently used in drug research programs by the pharmaceutical industry (4). Matsumori (5) and Goodwin (6) present reviews of animal models of cardiomyopathy, a subject which will be discussed later in this paper.

While no attempt is made to re-review the literature, there will be a survey of the more important etiologies of heart failure and a discussion of the relationships between the animal model and relevant clinical conditions.

2. EXPERIMENTAL MODELS OF HEART FAILURE

The basic physiological mechanisms in heart failure take several major forms: Pressure overload, volume overload, myocardial infarction, cardiomyopathy and other mechanisms. These will be discussed in some detail with reference to recent publications used to illustrate the latest models and concepts.

2.1. Pressure Loading

Pressure overloading can be observed in various experimental models. These include pulmonary banding, aortic constriction, aortic valve stenosis, pulmonary valve stenosis, experimental hypertension, and other forms.

Williams (7) showed that cats who were pulmonary artery banded responded positively to digoxin which reduced mortality when administered for 6 to 24 weeks after surgery. Contractile function of papillary muscles from hearts of animals in failure exhibited depressed contractile activity, but cats surviving the procedure by 24 weeks had normal papillary muscle activity. Recovery of contractile function was also enhanced by digoxin treatment. Dogs with experimental thoracic caval constriction (8) developed ascites

and edema. Captopril, 10 mg/kg, caused a striking decrease in plasma aldosterone (ALDO) concentration. Sodium excretion rose, mean arterial blood pressure (MABP) and filtration fraction decreased; plasma renin activity (PRA) increased. Daily administration of the drug decreased plasma ALDO levels and increased sodium excretion. Thus, like man, this model is sensitive to the effects of ACE inhibition. Rabbits of young and old ages were studied by Frolkis (9) who placed rings around the aorta to reduce the lumen by 2 to 2.5-times. Normal ageing changes, without coarctation, showed decreased cardiac output (CO), stroke volume (SV), and increased peripheral vascular resistance (PVR). There was decreased cardiac contractility and work, with a general deterioration in cardiovascular performance. Younger animals exhibited little response to aortic coarctation but older animals developed objective signs of cardiovascular disease such as immediate decreased minute volume, SV, cardiac index, dP/dt max and contractility index. Forty percent die within two to three days post-surgery characterized by acute cardiac insufficiency, pulmonary edema, hemorrhages into the myocardium and exudate into thoracic and abdominal cavities and blood congestion in the liver. Metabolic and ultrastructural changes caused by age and surgery in older animals are similar. Riegger (10) induced heart failure in dogs by rapid pacemaker stimulation for 14 days. The model was one of low output failure with a reduction in CO of 54%. Pulmonary artery (PAP) and pulmonary capillary wedge pressure (PCWP) rose, as did PRA, angiotensin (ANGIO), ALDO, epinephrine (EPI) and norepinephrine (NEPI) levels. Antidiuretic hormone (ADH) concentrations also rose but all parameters returned towards normal

when pacemaker stimulation was terminated. Belenkii showed that rats with aortic stenosis given inosine for 10.5 months did not develop full congestive heart failure (CHF) as did their untreated counterparts (11) indicating that administration of high energy phosphate compounds might be of potential benefit in human CHF. Raczniak (12) showed that administration of monocrotaline pyrrole causes pulmonary hypertension in rats after 4 weeks of treatment which becomes severe by 6 weeks. Respiratory function of heart mitochondria is markedly impaired at the later stages of failure. A stable model of ventricular failure in calves was developed by partial aortic occlusion. The model is particularly suited to studying the functions of aortic assist devices (13). Morris showed that rabbits with CHF produced by constriction of the abdominal aorta and administration of 10 meq of sodium per day caused progressive increases in MABP, PRA, ANGIO, ALDO and plasma sodium (14). Ohhara (15) developed a model of CHF in the halothane anesthetized dog with occlusion of the left anterior descending (LAD) coronary artery given dextran and propranolol. Isosorbide dinitrate is active in this preparation to reduce the effects of acute CHF.

2.2 Volume Loading

Models of this type of heart failure include fluid overload, aorta-to-vena cava fistula, aortic valve incompetence and atrial septal defect, among others. Belenkie (16) performed an aorta-to-left atrial shunt procedure in dogs. He found the animals developed a left ventricular volume overload and the animals

eventually died in pulmonary edema. Outcome was not predictable by echocardiography or ventricular performance and left ventricular function was enhanced or normal. Flaim (17), (18), (19) studied a high cardiac output rat model (HCO) produced by an aorta-caval fistula. Nitroglycerin was more potent as a regional vasodilator in the HCO than in normal (N) animals. Alterations in physiological parameters by the rats include significant bilateral ventricular hypertrophy and increased sympathetic tone via catecholamine secretion. Regional circulatory changes include maintenance of cerebral, coronary and hepatic flows at the expense of the muscle, cutaneous, renal and splanchnic beds. Nitroglycerin reduced SVR at rest but not during exercise. Porter (20) prepared dogs with chronic aorta-caval fistulas. The calcium antagonist diltiazem depressed left ventricular function in these animals but nitroprusside significantly reduced end diastolic dimensions and pressure without altering dP/dt max. Kirk (21) worked with a dog model of heart failure produced by a combination of acute coronary ligation, volume overload and propranolol. Both nitroglycerin and digitalis reduced LVEDP and increased myocardial blood flow. Koch (22) showed that high cardiac output failure in rats produced by aorta-vena cava anastomosis had renal hemodynamics similar to human CHF. The model had an impaired ability to excrete water due in part to increased ADH activity. Chong (23) used an anesthetized dog model prepared by intravenous infusion of lidocaine, 2%, at a rate of 1 ml/min. Dogs were first loaded with dextran 40 (10%) or dextran 70 (6%) in a bolus until CO, central venous pressure (CVP), PCWP, LVEDP were elevated. Milrinone 100 mcg/kg i.v. led to dramatic reversal of CHF parameteres. Niebauer (24) used dogs with

chronic (8-20 wks) aorta-cava fistula. These dogs had elevated heart rate (HR) and LVEDP and increased pulse pressure compared to N animals. Carotid sinus neural discharge curves indicated baroreceptor resetting and no change in sinus elasticity as demonstrated by phsical strain/pressure relationships of the carotid sinus wall. Mandin (25) produced a dog model of reversible cardiac edema by injecting and removing Freund's adjuvant as necessary, into the pericardial space. The tamponade resulting from this procedure caused edema and ascites. The model provided for a quick reversal of CHF.

2.3 Myocardial Infarction

Myocardial infarction has been produced by various methods including sustained atrial pacing, coronary ligation, controlled occlusions, coronary embolii, thrombus generation and controlled hypoxia. The most recent models are those by Kittleson (26) and Nuttall (27). Kittleson injected dogs with microspheres into the left circumflex coronary artery. Animals developed failure after 5 days. Hydralazine 1 mg/kg p.o. reduced systemic resistance index and which caused benefit to other cardiovascular parameters. Nuttal injected sephadex beads into the same artery in minipigs and found the platelet aggregation inhibitor, ticlopidine, produced a marked reduction in infarct size. This illustrated a model in which drugs with this mode of action may be beneficial prophylactically against heart failure produced by thrombus generation.

2.4 Cardiomyopathy and Other Models

The most widely known cardiomyopathy model is the Bio 14.6 Syrian hamster, but there are others which will be discussed first. Laky (28) showed that large subcutaneous injections of isoproterenol (10 mg/kg/day) or incomplete aorticligature in rats and guinea pigs produces a myocardial lesion-type heart failure. Liu (29) reviewed the literature on feline and canine hypertrophic cardiomyopathy and turkey and hamster cardiomyopathy discussing the physiology and pathophysiology of these models. Tomlinson (30) discussed experimental infective endocarditis induced in rabbits by streptococcus veridans. Papillary muscles from these animals showed an increase in myofibrillar size and interstitial edema. The muscles also exhibited focal necrosis, loss of myocardial architecture, and ultrastructural changes such as swelling and destruction of the mitochondria, sarcotubular system and separation of the intercalated discs. Tomlinson (31) also discussed the same rabbit model showing that serum enzyme levels of CPK, LDH and GOT levels were elevated. Cardiac contractile force as measured by force developed per gram of resting tension showed that contractility occured on the descending portion of the Starling curve. Reyes (32) showed permanent myocardial injury in a potential mouse model of cardiomyopathy when the animals were infected with coxsackievirus B3 (CB3). Unverferth (33) demonstrated that cobalt sulfate administered i.v. at a dose of 5 mg/kg/day to dogs caused a cardiomyopathy characterized by tachycardia, decreased dP/dt max, depressed ejection fraction and decreased MABP. There were no changes in cardiac index (CI) or

LVEDP. Redistribution of regional blood flows occured in that epicardial flow increased more than endocardial. Rona also showed that cobalt sulfate administered to rats (34) by daily gavage at a dose of 4.0-12.5 mg/kg was particularly effective when animals were preconditioned by a protein-free diet. Addition of DL-methionine and L-cystine to the diet protected cardiocytes from damage and prevented valvular lesions. Van Fleet (35) showed that furazolidone caused congestive cardiomyopathy in ducks which was reversible on cessation of administration. When the compound was administered in feed, the drug caused 30% mortality by 14 days and 60% by 28 days. While there was no evidence of myocardial necrosis, there was ascites, hepatic congestion, pericardial transudates, cardiac dilation and wall thinning.

Tilley (36) described the similarities of heart failure in cats and man. Of 4933 animals brought to necropsy at The Animal Medical Center in New York City recently, 421 showed spontaneous cardiomyopathies including endocarditis and myocarditis, congestive cardiomyopathy, symmetric and assymmetric hypertrophic cardiomyopathy, and restrictive cardiomyopathy. In comparison with the human disease the mature male cat has acute onset of dyspnea and/or aortic thromboembolism, gallop rhythm and systolic murmur, cardiomegaly and pulmonary edema. There is also abnormal ECG, elevated LVEDP, angiographic evidence of mitral regurgitation and other human-type pathology. The author urges the use of these animals in the investigation of the clinical disease.

Staley (37) investigated spontaneous congestive cardiomyopathy,

called Round Heart Disease, in turkeys. Treatment with propranolol, 2 mg/kg/day for 1 month produced diminished mortality. Studies on Ca++ transport indicated reduced Ca++ binding in the sarcoplasmic reticulum of birds treated with the beta blocker. Dunnigan (38) investigated the same cardiomyopathy in turkeys. This model of dilated cardiomyopathy was susceptible to programmed electrical stimulation which caused the onset of tachyarrhythmias, including VT. The author thinks that this model might be of use in the investigation of human CHF. Ueda (39) investigated a new subset of the well-known spontaneous hypertensive rat (SHR) which is already known to exist in a stroke-prone variety (SHRSP). The newest subset is known as heart-prone (SHRHP), which die the earliest of the varieties, from heart failure. The failure seems to occur as a result of inherited myocardial hypoxia due to hypertrophy and arteriosclerosis. There is fatty degeneration of the myocardial cells and sclerosis of the coronary arteries. The model may serve as a new approach to evaluation of experimental compounds. Arnolda (40) showed that chronic administration of the anti-cancer drug adriamycin (1 mg/kg) twice weekly intravenously to rabbits resulted in toxicity similar to that found in treated patients. He studied renal dynamics during the development of the heart failure. Failure occured with 8 weeks and resulted in a faster than normal increase in heart weight with pericardial effusions, ascites and hepatic congestion. Cardiac output and MABP fell and TPR rose. Renal blood flow fell about 40%; renal vascular resistance as well as PRA increased. After 4 wks NEPI rose suggesting vasoconstrictor mechanisms at work in this model of low output failure.

The cardiomyopathic (CM) Syrian hamster has been the most studied model of spontaneous cardiomyopathy. Various strains are now available, but most information is available on the Bio 14.6 strain. These animals develop a progressive cardio- myopathy leading to death much earlier than their N counterparts. Two important biochemical aspects of the developing heart fialure in the Syrian hamster have been studied by Schwartz (41). He found that Ca++ binding to the cardiac relaxing system (CRS) is actually less than in control (normal (N)) animals and duing the latter stages, as expected, mitochondrial show a decrease in number and diminished respiratory function. Sole (42) found that rate constants for NEPI turnover were very high in CM animals and NEPI content fell. Stress produced further decrease in NEPI content but ganglionic blockade effectively reversed this phenomenon. He concluded that increased sympathetic tone in HF causes a decrease in cardiac NEPI contnet and when sympathetic reserve is lost HF is manifested. Sved (43) found that arginine vasopressin (AVP) levels in CM hamsters were reduced by two-fold compared to aged matched controls. Antagonists to AVP decreased vasomotor tone and caused a fall in MABP. AVP levels may contribute to the cardiovascular status of Bio 14.6 hamsters and this may also be the case in human CHF.

Hemodynamics in the pentobarbital anesthetized Bio 14.6 hamster was studied by Abelmann (44) who found that CHF in this animal is characterized by bradycardia, elevation of end diastolic pressure in both ventricles, decrease in left ventricular systolic pressure and increase in right ventricular systolic pressure. There was no

difference in oxygen consumption but the arterio-venous (A-V) difference was narrower in CM animals; thus the failure is the high output type. Cantin (45) studied electrolyte shifts in the CM hamster and Chimosky (46) found that hearts of these animals at 220 days of age are deficient in atrial naturetic factor (ANF) and that saline extracts of atria produce one-third the natriuretic and diuretic effects of extracts of atria from N hamsters. These results suggested that ANF might be a humoral mediator, the deficiency of which might contribute to venous congestion and edema found in the CM animal. Dhalla (47) studied sarcolemmal Ca++, Mg++, and Na-K ATP-ase which increased in late stages of the CM hamster's development of HF. Wikman-Coffelt (48) found that the calcium antagonist verapamil given in drinking water protected half to three-quarters of the CM hamsters from early death. Evidence was also presented that ADP, ATP and phosphocreatine/creatine ratios were beneficially altered by verapamil treatment. Gertz (49) fragmented the sarcoplasmic reticulum from N and CM animals. The ATP dependent CA++ oxalate pumping of the SR was not different from N in CM at 10 days but was markedly reduced (78%) at 300 days at the time of severe failure. Nevertheless CA++ oxalate capacity per unit of SR was unchanged suggesting dilution of SR by the resultant hypertrophy. Cantin (50) studied renal function and structure in HF in CM hamsters. He found that ultrastructural and glomerular changes occur late in HF. Elevation of serum proteins and hemodilution, both of which occur in man, is similar. Horvath (51) studied the hypothalamic-hypophyseal system in the CM hamster which showed a decreased pituitary weight in early stages of HF but in later phase neurohypohysis is swollen with depletion of

neurosecretory material, suggesting increased production and release of posterior lobe hormones. Nadkarni (52) showed by ultrastructural analyses of the CM hamster heart that there were delayed or defective genesis of contractile elements, with consistent mitochondrial abnormalities and elevated serum and tissue Ca++ levels. Schwartz (53) showed that intracellular pH alterations in the CM hamster heart may alter the affinity of subcellular organelles to Ca++.

Hearts of CM hamsters have higher Tyrosine hydroxylase (TH) levels than matched N animals according to Sole (54). Sordahl (55) found that a depletion of high energy phosphates in the CM hearts occurs, while Tapp (56) found that cold-restraint-electric-shock-stress exacerbates HF peripheral manefestations in CM but not N hamsters.

While much work has been done to establish the CM hamster as a significant model of human HF there have been other models used as primary and secondary test objects. Lund (57) studied a dog model of right heart failure in which he found abnormal reflex sympathetic and parasympathetic control of the heart. He studied the enzymes responsible for part of the synthetic pathways for NEPI and acetylcholine. In dogs with surgically induced tricuspid insufficiency and pulmonary stenosis prepared two years earlier he found reduced TH and dopamine-beta hydroxylase activities in the heart. Like the CM hamster, NEPI content was markedly diminished, with loss of enzyme activity associated with these changes. Choline acetyltransferase activity was not affected however. Both the stressed right ventricle and non stressed left ventricle were

equally affected. The left, but not the right atrium showed significant reduction in both synthetic enzymes suggesting non-uniform alterations in neural control in chronically diseased hearts. In further experiments Lund (58) indicated that parasympathetic control in the failing human heart is impaired so he investigated neural control in various animal models of HF. He measured cholineacetyltransferase (CAT) activity in hearts of hamsters with skeletal myopathy and CM, in dogs with pulmonary artery constriction and tricuspid evulsion and guinea pigs with pulmonary artery constriction. TH activity and DBH activity and NEPI levels served as indices of sympathetic innervation. In myopathic hearts, total CAT activity was normal in contractile and specialized tissues. In all three models indices of sympathetic innervation were altered in ways qualitatively different from parasympathetic indices. TH and DBH activities were increased in myopathic ventricles, decreased in hypertrophied dog and guinea pig ventricles and non hypertrophied dog ventricles and normal and non hypertrophied guinea pig ventricles.

MacCannel (59) found that urotensin, a vasoactive peptide from fish causes mesenteric dilation in dogs and should be a good afterload reducing agent. Pentobarbital anesthetized dogs in heart failure as a result of chronic aortico-left atrial shunt were used. Equidepressor doses of sodium nitroprusside and urotensin produced comparable falls in TPR, LVEDP, PCWP. Nitroprusside, but not urotensin did not cause underperfusion of vital organs.

Vatner (60) studied alterations in myocardial beta receptor

adenylate cyclase activity as well as muscarinic receptor density in a dog model of left ventricular failure (aortic stenosis). Muscarinic receptor density fell and this may be mechanism of altered parasympathetic control in failing hearts. Villareal (61) found that prostaglandins may be involved in the maintenance of renal blood flow in a dog model of high output failure. Newman (62) found that myocardial taurine is elevated in patients dying from CHF and is elevated in animal models such as hypertrophied ventricles of rats with stress-induced or spontaneous hypertension. In dogs with CHF induced by creating an infrarenal aortocaval fistula, taurine levels and PCWP elevations were positively correlated. Mercadier (63) studied myosin isoenzyme changes in several models of rat cardiac hypertrophy which showed changes in myosin in rat heart were in response to mechanical overloading.

Datta (64) found that postweanling rats fed a diet of milk and sugar develop an anemia where hemoglobin levels fall to less than 30% in 8 to 10 weeks. This produces an anemic cardiomegaly. He found that chronic anemia especially with increased workload produces a model of functional and biochemical cardiac deterioration.

In isolated tissue experiments, Fein (65) showed that papillary muscles from rats with renovascular hypertension and streptozotocin-induced diabetes were a good model to study mechanical properties of the failing heart. Alousi (66,67) measured catecholamine, protein and RNA in isolated perfused CM

hamster hearts. The rate of protein and RNA synthesis was reduced in CM hearts. Ouabain and NEPI were very active in this preparation of a failing heart. Kannengiesser (68) showed that isolated perfused rat hearts with coronary artery occlusion with microspheres is a stable sensitive preparation of HF.

3. CONCLUSIONS

The array of intact and isolated models of HF seems to indicate that there are several useful approaches to evaluating particular aspects of failure. These can provide information not easily obtained in the clinic setting, and may be useful in the search for new therapeutic compounds. One should keep in perspective that any one model can only be used to answer a particular question, or test a mechanism of action, rather than predict overall success in man. It is apparent that pharmacological approaches can contribute much towards the success of drug research in human heart failure.

REFERENCES

1. Opie, L.H., Walpoth, B. and Barsacchi, R. Calcium and catecholamines: relevance to cardiomyopathies and significance in therapeutic strategies. J. Mol. Cell. Cardiol. 17 21, 1985.

2. Pouleur, H. Future treatment of chronic heart failure. Third World Conference on Clinical Pharmacology and Therapeutics. Stockholm, Sweden 1986.

3. Smith, H.J. and Nutall, A. Experimental models of heart failure. Card. Res. 19 181, 1985.

4. Evans, D.B., Weishaar, R.E. and Kaplan, H.R. Strategy for the discovery and development of a positive inotropic agent. Pharmacol. Ther. 16 303, 1982.

5. Matsumori, A. and Kaiwai, C. Animal models of cardiomyopathy. Int. J. Cardiol. 3 368, 1983.

6. Goodwin, J.F. Mechanisms in cardiomyopathies. J. Mol. Cell. Cardiol. 17 215, 1985.

7. Williams, J.F. and Potter, R.D. The effect of chronic digitoxin administration on the contractile state of normal and non failing hypertrophied myocardium. J. Clin. Invest. 56 71, 1975.

8. Freeman, R.H., Davis, J.O., Williams, G.M., DeForrest, J.M., Seymour, A.A. and Rowe, B.P. Effects of the oral converting enzyme inhibitor, SQ 14225, in a model of low cardiac output in dogs. Circ. Res. 45 540, 1977.

9. Frolkis, K.V., Bogatskaya, L.N., Stupina, A.S. and Shevchuk, V.G. Experimental analysis of development of cardiac insuficiency in old age. Am. Heart J. 93 334, 1977.

10. Riegger, A.J. and Liebau, G. The renin-angiotensin-aldosterone system, antidiuretic hormone and sympathetic nerve activity in an experimental model of congestive heart failure in the dog. Clin. Sci. 62 465, 1982.

11. Belenkii, E.E., Solkolov, I.K., Kleimenova, N.N., Suzdalnitskii, R.S. and Tunitskay, T.A. Prevention of chronic experimental heart insufficiency by inosine. Cor Vasa 17 57, 1975.

12. Roczniak, T.J., Chesney, C.F. and Allen, J.R. Oxidative phosphorylation and respiration by mitochondria from normal, hypertrophied and failing rat hearts. J. Mol. Cell. Cardiol. 9 215, 1977.

13. Cant, J.R. and Chimoskey, J.E. Left Ventricular failure in calves produced by supravalvular aortic stenosis. Biomat. Med. Dev. Art. Org. 5 379, 1977.

14. Morris, B.J., Davis, J.O., Zatzman, M.L. and Williams, G.M. The renin-angiotensin-aldosterone system in rabbits with congestive heart failure. Nippon Yakurigaku Zasshi. 82 343, 1983.

15. Ohhara, H., Takeda, M., Igarashi, T. Effects of intravenous infusion of isosorbed dinitrate (ISDN) on hemodynamics of dogs with congestive heart failure. Nippon Yakurigaku Zasshi. 82 343, 1983.

16. Belenkie, I., Baumber, J.S., and Rademaker, A. Changes in left ventricular dimensions and performance resulting from acute and chronic volume overload in the conscious dog. Can. J. Physiol. Pharmacol. 61 1274, 1983.

17. Flaim, S.F., Minteer, W.J., Nellis, S.H. and Clark, D.P. Chronic arteriovenous shunt: evaluation of a model for heart failure in rats. Am J Physiol. 236 H698, 1979.

18. Flaim, S.F., Weitzel, R.L. and Zelis, R. Mechanism of action of nitroglycerin during exercise in a rat model of heart failure. Circ. Res. 49 458, 1981.

19. Flaim, S.F. Peripheral vascular effects of nitroglycerin in a conscious rat model of heart failure. Am. J. Physiol. 243 H974, 1982.

20. Porter, C.B., Walsh, R.A., Badke, F.R. and O'Rourke, R.A. Differential effects of diltiazem and nitroprusside on left ventricular function in experimental chronic volume overload. Circulation 68 685, 1983.

21. Kirk, E., LeJemtel, T.H., Nelson, G.R. and Sonnenblick, E. Mechanisms of beneficial effects of vasodilators and inotropic

stimulation in the experimental failing ischemic heart. Am. J. Med. 65 189, 1978.

22. Koch, K.M., Frei, U., Kunkel, B. and Meyer-Sabellek, W.A. High output cardia failure in rats. Contrib. Nephrol. 19 155, 1980.

23. Chong, L.J., Smith, T.D. and Povzhitkov, M.M. A new model of congestive heart failure in anesthetized dogs. Proc. west. Pharmacol. Soc. 28 81, 1985.

24. Niebauer, M. and Zucker, I.H. Static and dynamic responses of carotid sinus baroreceptors in dogs with chronic volume overload. J. Physiol. 369 295, 1985.

25. Mandin, H., Alexander, F. and Kirsten, J. An animal model of reversible cardiac edema. Kidney Int. 7 (6) 433, 1975.

26. Kittleson, M.D. and Hamlin, R.L. Hydralazine pharmacodynamics in the dog. Am. J. vet. Res. 44 1501, 1983.

27. Nuttall, A., Smith, H.J. and Loveday, B.E. A clinically relevant model of heart failure: effects of ticlopidine. Card. Res. 19 187, 1985.

28. Laky, D., Constantinescu, S., Filipescu, G., Ratea, E. and Zeana, C. The biology of the myocardium in chronic hypoxia. Morphol. Embryol. 31 295, 1985.

29. Liu, S.K. and Tilley, L.P. Animal models of primary myocardial diseases. Yale J. Biol. Med. 53 191, 1980.

30. Tomlinson, C.W. and Dhalla, N.S. Myocardial cell damage during experimental infective endocarditis. Lab Invest. 33 316, 1975.

31. Tomlinson, C.W. and Dhalla, N.S. Alterations in myocardial function during bacterial infective cardiomyopathy. Am. J. Cardiol. 37 373, 1976.

32. Reyes, M.P., Smith, F.E. and Lerner, A.M. An enterovirus-induced model of an acute dilated-type cardiomyopathy. Intervirology 22 146, 1984.

33. Unverferth, D.V., Croskery, R.W., Leier, C.V., Altschuld, R., Pipers, F.S., Thomas, J., Magorien, R.D. and Hamlin, R.L. Canine cobalt cardiomyopathy: A model for the study of heart failure. Am.J. vet. Res. 44 989, 1983.

34. Rona, G. & Chappel, C.I. Pathogenesis and pathology of cobalt cardiomyopathy. Recent Adv. Stud. Card. Struct. Metab. 2, 407 1973

35. Van Fleet, J.F. and Ferrans, V.J. Furazolidone-induced congestive cardiomyopathy in ducklings: Regression of cardiac lesions after cessation of furazolidone ingestion. Am.J. vet. Res. 44 1007, 1983.

36. Tilley, L.P., Liu S.K. The striking similarity between myocardial disease in cats and man. Med. Times 106 2d, 1978.

37. Staley, N.A., Noren, G.R., Einzig, S. and Rublein, T.G. Effect of early propranolol treatment in an animal model of congestive cardiomyopathy: I Mortality and Ca++ transport in sarcoplasmic reticulum. Card. Res. 18 371, 1984.

38. Dunnigan, A., Noren, G.R., Einzig, S. and Benditt, D.G. Inducible ventricular arrhythmias in a naturally occuring model of cardiomyopathy. Card. Res. 18 645, 1984.

39. Ueda, H., Miyazaki, T., Suganuma, Y., Saito, N. and Kato, Y. Cardiac death and myocardial lesions in non-stroke SHRSP under specific pathogen-free system. Jpn. Heart.J. 22 387, 1981.

40. Arnolda, L., McGrath, B., Cocks, M., Sumithran, E. and Johnston, C. Adriamycin cardiomyopathy in the rabbit: an animal model of low output cardiac failure with activation of vasoconstrictor mechanisma. Cardiovascular Res. 19 378, 1985.

41. Schwartz, A., Sordahl, L.A., Crow, C.A., McCollum, W.B., Harigaya, S. and Bajusz, E. Several biochemical characteristics of the cardiomyopathic Syrian hamster. Recent Adv. Stud. Card. Struct. Metab. 1,235 1972.

42. Sole, M.J., Wurtman, R.J., Lo, C.M., Kamble, A.B. and Sonnenblick, E.H. Tyrosine hydroxylase activity in the heart of

the cardiomyopathic Syrian hamster. J. Mol. Cell. Cardiol. 9 225, 1977.

43. Sved, A.F., Ottenweller, J.C., Tapp, W.N. and Thompson, M.E. Elevated plasma vasopressin in cardiomyopathic hamsters. Life Sciences 37 2313, 1985.

44. Abelmann, W.H., Jeffrey, F.E. and Wagner R. Hemodynamics of the hereditary cardiomyopathy of Syrian hamsters. Recent Adv. Stud. Card. Struct. Metab.1, 225

45. Cantin, M. Forthomme, D. and Bajusz, E. Renal Glomerulus in experimental congestive heart failure: ultrastructural and functional study. Recent Adv. Stud. Card. Struct. Metab.2,467 1973.

46. Chimoskey, J.E., Spielman, W.S., Brandt, M.A. and Heidmann, S.R. Cardiac atria of Bio 14.6 hamsters are deficient in natriuretic factor. Science 223 820, 1984.

47. Dhalla, N.S., Tomlinson, C.W., Singh, J.N., Lee, S.L., McNamara, D.B., Harrow, J.A.C. and Yates, J.C. Role of sarcolemmal changes in cardiac pathophysiology. Recent Adv. Stud. Card. Struct. Metab. 9, 377 1972.

48. Wikman-Coffelt, J., Sievers, R., Parmley, W.W. and Jasmin, G. Verapamil preserves adenine nucleotide pool in cardiomyopathic Syrian hamster. Am.J. Physiol. 250 H22, 1986.

49. Gertz, F.W., Stam, A.Jr., Bajusz, and Sonnenblick, E. A biochemical defect in the function of the sarcoplasmic reticulum in the hereditary cardiomyopathy of the Syrian hamster. Recent adv. Stud. Card. Struct. Metab. 1,243 1972.

50. Cantin, M., Leone, A. and Bajusz, E. Participation of renal electrolytes in the mechanism of edema in congestive heart failure: studies on cardiomyopathic Syrian hamsters. Recent Adv. Stud. Card. Struct. Metab. 1, 303 1972.

51. Horvath, E. Bajusz, E. and Kovacs, K. Study of the hypothalmic-hyopophyseal system in hereditary cardiomyopathic hamsters. Recent Adv. Study Cardiac Sturct. Metab. 1 294, 1972

52. Nadkarni, B.B., Hunt, B. and Heggtveit, H.A. Early ultrastructural and biochemical changes in the myopathic hamster heart. Recent Adv. Stud. Card. Struct. Metab. 1, 251 1972.

53. Schwartz, A. Biochemical studies concerning etiology of hypertrophy, heart failure and cardiomyopathy. Recent Adv. Study Cardiac Struct. Metab. 2 501, 1973

54. Sole, M.J., Lo, C.M., Laird, C.W., Sonnenblick and Wurtman, R.J. Norrpinephrine turnover in the heart and spleen of the cardiomyopathic Syrian hamster. Circ. Res. 37 855, 1975.

55. Sordahl, L.A. Some biochemical lesions in myocardial disease. Tex. Rep. Biol. Med. 38 121, 1979.

56. Tapp, W.N., Levin, B.E. and Natelson, B.H. Stress-induced heart failure. Psychosom. Med. 45 171, 1983.

57. Lund, D.D., Schmid, P.G., Johannsen, U.J. and Roskoski, R.Jr. Biochemical indices of cholinergic and adrenergic autonomic innervation in dog heart: disparate alterations in chronic right heart failure. J.Mol. Cell. Cardiol. 14 419, 1982.

58. Lund, D.D., Schmid, P.G., and Roskoski, R.Jr. Neurochemical indices of autonomic innervation of heart in different experimental models of heart failure. Adv. Exp. Med. Biol. 161 179, 1983.

59. MacCannel, K.L., Giraud, G.D., Lederis, K., Hamilton, P.L. and Groves, G. Effect of a specific and non specific vasodilator on regional blood flows in experimental heart failure. Can.J. Physiol. Pharmacol 60(2), 174 1982.

60. Vatner,D.E., Vatner, S.F., Fujii, A.M. and Homcy, C.J. Loss of high affinity cardiac beta adrenergic receptors in dogs with heart failure. J.Clin. Invest. 76 2259, 1985.

61. Villareal, D., Davis, J.O., Freeman, R.H., Dietz, J.R. and Echtenkamp, S.F. Effects of indomethacin in conscious dogs with experimental high-output heart failure. Am.J. Physiol. 245 H942, 1983.

62. Newman, W.H., Frangakis, C.J., Grosso, D.S. and Bressler, R. A relation between myocardial taurine content and pulmonary wedge

pressure in dogs with heart failure. Physiol. Chem. Phys. 9 259, 1977.

63. Mercadier, J.J., Lompre, A-M., Wisnewsky, C. Samuel, J-L., Bercovici, J.B., Swynghedauw, B. and Schwartz, K. Myosin isoenzymic changes in several models of rat cardiac hypertrophy. Circ. Res. 49 525, 1981.

64. Datta, B.N. and Silver, M.D. Cardiomegaly in chronic anemia in rats. Lab. Invest. 32 503, 1975.

65. Fein, F.S., Capasso, J.M., Aronson, R.S., Cho, S. and Nordin, C. Combined renovascular hypertension and diabetes in rats: a new preparation of congestive cardiomyopathy. Circulation 70 318, 1984.

66. Alousi, A.A. and Beards, J.A. Catecholamine, protein, and RNA content in advanced congestive heart failure in the Syrian hamster. Recent Adv. Study Cardiac Struct. Metab. 1 279, 1973.

67. Alousi, A.A. and Santa Barbara, L. Effects of ouabain and norepinephrine on the mechanical performance of the normal and failing heart of the myopathic hamster. Recent Adv. Stud. Card. Struct. Metab. 1, 421 1972.

68. Kannengiesser, G.J., Lubbe, W.F. and Opie, L.H. Experimental myocardial infarction with left ventricular failure in the isolated perfused rat heart. Effects of isoproterenol and pacing. J. Mol. Cell. Cardiol. 7 135, 1975.

7

ELECTROPHYSIOLOGY IN CONGESTIVE HEART FAILURE ANIMAL MODELS

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As the physiologic end-stage of a variety of cardiac pathologies, heart failure has increased in incidence over the last decade in part because of earlier recognition of the provoking pathology and improved hospital and intensive care treatment. In spite of multiple interventional studies directed to the correction of hemodynamic abnormalities and the improvement of functional capacity, patients with heart failure continue to have a high annual mortality rate. In a recent prospective study of patients with severe chronic heart failure, Wilson and Horowitz et al. demonstrated an average mortality rate of 20% per year (1). In these patients, cardiac mortality was divided equally between sudden death and pump failure. While the only clinical or hemodynamic variable that correlated with survival was a functional class, the extremely high incidence of complex ventricular arrhythmias in these patients may be a consequence of the overall severity of circulatory dysfunction. While sudden death may be the consequence of lethal ventricular arrhythmias, pump failure may be the consequence of the deleterious hemodynamic consequences of non-lethal arrhythmias. Non-sustained ventricular tachyarrhythmias could perturb previously compensated cardiac output by adversely shortening diastolic filling time, increasing oxygen consumption and metabolic requirements and

decreasing the atrial contribution to cardiac output. On the other hand, bradyarrhythmias could severely depress cardiac output in the poorly compensated heart with little cardiac reserve. In this sense, the presence of complex ventricular arrhythmias may be a marker for both sudden death and pump failure in patients with congestive heart failure. In spite of the potential importance of these observations, there is relatively little information regarding the possible arrhythmogenic mechanisms of heart failure.

Animal models offer some important advantages for the study of the electrophysiologic abnormalities associated with heart failure. Unlike clinical studies, the experimental protocol, the animal population and the mechanisms for the induction of heart failure can be precisely controlled in animal studies. However, in all animal models it is often problematic to extrapolate experimental results to conclusions regarding human physiology. Although all animal models are "wrong" to the degree they deviate from the human clinical situation, they nevertheless can provide useful information. The various models differ predominantly in respect to the mechanism for the induction of heart failure. A volume overloaded state can be created as a consequence of valvular insufficiency, both tricuspid and mitral. A pressure overloaded ventricle can be induced by right or left ventricular outflow obstruction with either pulmonary artery or aortic banding. Rapid ventricular pacing or myocardial toxins such as adriamycin, pentobarbital or cobalt have been employed to duplicate the physiology of heart failure. There are also naturally occuring models of spontaneous failure such as the congenital cardiomyopathic

Syrian hamster and "round heart disease" in turkeys.

Recent studies of several of these congestive heart failure models have demonstrated multiple in vitro and in vivo electrophysiological abnormalities suggestive of one or both the principal mechanisms of arrhythmogenesis: reentry and enhanced automaticity. With specific regard to reentry, several of the abnormal conditions required to sustain a reentrant circuit have been demonstrated such as 1) unidirectional block 2) enhanced excitability 3) altered refractoriness and 4) abnormal conduction velocities. Using an in vitro model of ventricular hypertrophy without failure Aronson described several electrophysiologic abnormalities with arrhythmogenic potential (2). Abnormalities of transmembrane action potentials from hypertensive rat papillary muscles included prolonged action potential durations, early and late afterdepolarizations, and triggered spontaneous activity (3). In the cat and rat models, Gulch also observed this characteristic action potential prolongation and characterizes it as a function of cells exposed to high chronic wall stress in both hypertrophied and non-hypertrophied hearts (4). Importantly, in the absence of failure, other action potential parameters were normal. These included resting membrane potentials, action potential amplitudes, overshoot and maximal rate of rise of phase 0 depolarizations. As a consequence of chronic left ventricular pressure overload in the cat, Cameron et al. noted generalized cardiac hypertrophy with patchy endocardial fibrosis with marked connective tissue hyperplasia (5). These areas were characterized by multiple cellular electrophysiologic abnormalities that could serve as a

substrate for a reentrant mechanism of arrhythmogenesis. While areas of generalized hypertrophy were characterized by prolonged action potential durations, the areas of patchy fibrosis displayed a heterogeneous number of abnormalities including severely shortened action potential durations, slow potentials, depressed resting potentials and electrically silent areas. This evidence of electrical instability could lead to reentry and increased vulnerability to arrhythmias. In vitro electrophysiologic abnormalities of failure were evaluated by Gelband and Bassett in right ventricular failure resulting from pulmonary artery banding (6). In addition to the prolonged action potential durations noted above and associated with myocardial hypertrophy, they also observed decreased resting membrane potentials, diminished action potential overshoots and depressed maximum upstroke velocity. While the cellular electrophysiologic parameters are thought to be associated with the ion transport system of an electrogenic sodium-potassium pump, the exact mechanism for the altered and depressed electrical properties of right ventricular failure are not clear. Houser et al have shown that this ion transport system responds abnormally in hypertrophied and failing muscle (7). Failing myocardium was incapable of spontaneous normal rate related changes in membrane potential and this effect was not significantly ameliorated by the addition of epinephrine (8).

Using the Barger and Roe model of right ventricular failure as a consequence of sequential pulmonary artery constriction followed by experimentally induced tricuspid insufficiency (9), White et al. evaluated the in vivo consequences of the in vitro cellular

electrophysiologic abnormalities described above (10). They showed a marked increase in excitability threshold of both ventricles, even though failure was limited to the right side. These changes were paralleled by profound alterations in sympathetic autonomic function; circulating catecholamine levels were elevated while tissue norepinephrine and tyrosine hydroxalase activity were markedly less. In contrast to the correlation of in vitro cellular abnormalities to areas of unusual hemodynamic stress as noted by Gulch above, this in vivo elevation of excitability can not be attributed to mechanical stretch alone since ventricular dilitation was limited to the right ventricle and therefore unlikely to be a direct cause for the significant increase in the left ventricular excitability thresholds.

In conclusion, the several in vitro and in vivo animal models reviewed above have added to our understanding of the electrophysiologic abnormalities that accompany myocardial hypertrophy and failure. While they do not duplicate the clinical situation, they do approximate many of the complex physiologic alterations involved in heart failure. In spite of the encouraging results from these initial studies, it is still uncertain whether the high incidence of ventricular arrhythmias in patients with congestive heart failure is a marker for the severity of their underlying disease or a primary pathogenic event. Obviously, the answer to this question has important therapeutic implications apart from its scientific interest. It is certain that further extensive evaluation of these and other animal models will add significantly to our future understanding of the importance of arrhythmogenesis in

heart failure and ultimately will contribute to therapeutic modalities that will alter the present unacceptably high mortality rate in patients with heart failure.

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References

1. Wilson, JR, Schwartz JS, Sutton MSJ, Ferraro N, Horowitz LN, Reichek, N and Josephson, ME: Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. J. Am. Coll. Cardiol. 2:403-410, 1983.
2. Aronson RS. Characteristics of action potentials of hypertrophied myocardium from rats with renal hypertension. Circ. Res. 47:443-454, 1980.
3. Aronson RS. Afterpotentials and triggered activity in hypertrophied myocardium from rats with renal hypertension. Circ. Res. 48:720-727, 1981.
4. Gulch, RW. The effect of elevated chronic loading on the action potential of mammalian myocardium. J. Mol. Cell. Cardiol. 12:415-420, 1980.
5. Cameron JS, Myerburg RJ, Wong, SS, Gaide MS, Epstein K, Alvarez TR, Gelband, H, Guse PA and Bassett, AL: Electrophysiologic consequences of chronic experimentally-induced left ventricular pressure overload. J. Am. Coll. Cardiol. 2:481-487, 1983.
6. Gelband H, and Bassett AL. Depressed transmembrane potentials

during experimentally induced ventricular failure in cats. Circ. Res. 32:625-634, 1973.

7. Houser SR, Freeman AR, Falger JM, Breisch EA, Coulson RL, Carey R, and Spann JF: Resting potential changes associated with Na^{+}-K^{+} pumps in failing heart muscle. Am. J. Physiol. 240 (Heart Circ. Physiol. 9) H168-H176, 1981.

8. Houser SR, Burgis V, Martin F, and Weinberg D. Effect of epinephrine on resting potential in normal and hypertrophied cardiac muscles. Am. J. Physiol. 245 (Heart Circ Physiol 14) H90-H97, 1983.

9. Barger AC, Roe, BB and Richardson GS. Relation of valvular lesions and of exercise to auricular pressure, work tolerance and to development of chronic congestive failure in dogs. Am. J. Physiol. 169:384-399, 1952.

10. White, CW, Mirro, MJ, Lund, DD, Skorton, DJ, Pandian, NG and Kerber, RE. Alterations in ventricular excitability in conscious dogs during development of chronic heart failure. Am. J. Physiol. 250:H1022, 1986.

8

NONINVASIVE EVALUATION OF PROARRHYTHMIA

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A potential cardiac adverse reaction to drug therapy may be the induction or worsening of a brady or tachyarrhythmia. This is particularly the case for drugs that may have a direct action on cardiac electrophysiologic or hemodynamic parameters. In fact, all antiarrhythmic agents, though prescribed to suppress cardiac arrhythmias, have been documented to have the potential to aggravate or provoke arrhythmias.[1,2]

Since there is a marked spontaneous variability in the frequency and severity of ventricular arrhythmias[3] and since underlying cardiac disease may change with time, the differentiation of a provoked or new arrhythmia as an adverse effect from drug therapy (proarrhythmia) from a change in the natural history of the patient's underlying disease is often impossible. Nevertheless, an operational definition for proarrhythmia is essential for clinical research and regulatory purposes.

DEFINITION OF PROARRHYTHMIA

"Proarrhythmia" and "arrhythmogenesis" are the terms used to describe the worsening or the new onset of arrhythmias. It has been suggested that the term "arrhythmogenesis" be used for the creation

of an arrhythmia by any cause.[4] "Proarrhythmia" is the term that can be used for an arrhythmia which is drug-induced. A "provocation" of an arrhythmia is defined as the creation of a new arrhythmia by drugs whereas the "aggravation" of an arrhythmia is the worsening of a previously documented arrhythmia by drugs.

The difficulty in identifying proarrhythmia is in differentiating an arrhythmia which is unquestionably due to or made worse by drug therapy versus the lack of antiarrhythmic efficacy or spontaneous change in the patient's underlying clinical state. Since the mechanism of the cellular electrophysiologic changes responsible for proarrhythmia versus a spontaneous change have not been adequately studied nor have the pharmacological causes of proarrhythmia been established, only an arbitrary definition for proarrhythmia is possible.

Proarrhythmia may take the form of a brady or tachyarrhythmia or a change in an arrhythmia's frequency. Proarrhythmia is not an alteration in conduction that may manifest itself as first degree AV block, intraventricular conduction delay, or a prolongation of the QT or JT interval. A bradyarrhythmia such as sinus node exit block or sinus arrest can be a proarrhythmic response. Second or third degree AV block would be another example of a proarrhythmic bradyarrhythmia. The development of a tachyarrhythmia as a proarrhythmic response may manifest as either a supraventricular or ventricular tachyarrhythmia. The new occurrence or worsening of ventricular or atrial ectopy are other examples of proarrhythmia.

Certain proarrhythmic events can be related clearly to drug therapy while in other circumstances the same arrhythmic change may

be related to another factor. In the latter case the potentially offending drug does not necessarily need to be stopped since correction of the associated factor may often eliminate the "proarrhythmic" response. Proarrhythmia due clearly to drug toxicity requires that that drug be discontinued and further use of the offending agent is usually not recommended. This is analguous to an unpredictable idiosyncratic reaction such as allergic response to a drug. This type of proarrhythmic response should be considered "primary". When the apparent proarrhythmic response is due to another factor such as:

> Acute cardiac instability, e.g.: within 72 hours of an acute myocardial infarction acute, worsening of congestive heart failure due to change in sodium intake or alteration in anti-heart failure drugs, post-cardiac surgery, etc.
>
> or
>
> A change in the metabolic state, e.g.: the development of hypokalemia, hypomagnesemia, acidosis or alkalosis, etc.
>
> or
>
> New drug interactions

it should be considered a "secondary proarrhythmia".

As a means to help distinguish between proarrhythmia and a change in the underlying cardiac state, we have suggested that if the potential proarrhythmic response occurs after one month on a constant daily dose of the drug that primary proarrhythmia is unlikely. Others have suggested that this arbitrary one month cutoff period should be replaced with the time that the drug takes to reach steady-state. We prefer the one month criteria to err on

the conservative side so that primary proarrhythmia will not be underestimated. Another circumstance in which we would relegate a new or worsened arrhythmia to an alteration in the clinical state of the patient rather than a drug toxicity would be when the potential proarrhythmic response is observed on one day but not on subsequent days using the same detection methods. The only exception to this would be the development of sustained ventricular or supraventricular tachycardia since these rhythms may be paroxsymal.

Table 1 details the definition of proarrhythmia that we currently use which is derived from noninvasive electrocardiographic monitoring of spontaneous events. This definition details that the new onset of a ventricular arrhythmia (1A thru E) or an atrial arrhythmia (1F and G) would be considered a proarrhythmic response. Since no data exist to define the spontaneous variability of atrial premature complexes, we have omitted a consideration of a change in the frequency of isolated atrial premature complexes as part of the definition of proarrhythmia. Since noninvasive monitoring techniques do not usually quantitate atrial premature complex frequency and since the clinical impact of this rhythm is not considered serious we do not consider this omission to be important.

It is now been well demonstrated[5] that ventricular premature complexes (VPCs) occur less than 100 per day or less than 5 per hour in normal individuals. Thus, if a patient has not had any previously documented VPCs above this "normal level" and is placed on a drug and now has greater than 5 VPCs per hour this would be considered the new onset of VPCs and meet the definition for proarrhythmia. Likewise, in a patient who has never had

nonsustained ventricular tachycardia, the development of a single triplet would constitute a proarrhythmic response. Such definitions of proarrhythmia have far different clinical impact than the development of new sustained ventricular tachycardia with associated cardiac syncope. A classification to account for the clinical relevance of the proarrhythmic response will be discussed below.

VALIDATION OF THE FREQUENCY DEFINITION FOR PROARRHYTHMIA

Table 1 - Section 2 details an arbitrary algorithm to define the required increase in VPC frequency to detect proarrhythmia versus spontaneous variability.[2] A greater frequency increase is required when the baseline VPC frequency is low since spontaneous variability is greater when the baseline VPC frequency is low.[3] We have recently validated this algorithm by describing the degree of spontaneous variability in VPC frequency that occurred in 495 ventricular arrhythmia patients who had ≥2 Holter monitors sessions on placebo therapy. The same increase in VPC frequency that would be ascribed to proarrhythmia by the algorithm (Table 1, Part 2) occurred in 0/47 (0%) of patients with baseline VPC frequency of 10-50/hr, 3/44 (7%) with 51-100 VPCs/hr, 1/139 (0.7%) in 101-300 VPCs/hr and 1/265 (.04%) in VPC frequency >300/hr. Thus, 5/496 or 1% of patients would have been classified as having a proarrhythmia using this algorithm despite the fact that only placebo was given. In terms of the increase in the frequency of beats in the form of nonsustained ventricular tachycardia (Table 1 - 2B) we have found that a 10-fold increase in such events on placebo occurred in 9/274 (3%) of patients.[6] Thus, the frequency algorithm appears to be

useful in differentiating spontaneous variability from a proarrhythmic event.

Table 1 suggests 2 further phenomena that we define as proarrhythmia which are less objective than the new onset or change in frequency of an arrhythmia. These include a significantly more difficult cardioversion or termination of a ventricular tachyarrhythmia as defined by the treating physician. Drugs, such as flecainide and encainide which are potent suppressors of cardiac conduction have been associated with the development of a proarrhythmic response characterized by the more difficult or impossible cardioversion of a ventricular tachyarrhythmia that was previously easily terminated before the use of such antiarrhythmic agents.[2] To distinguish this phenomena from the terminal event in the natural history of a very ill cardiac patient requires physician judgment and experience since no quantitative measures can clearly be put to this parameter at this time. Fortunately the prevalence of such proarrhythmic events have markedly decreased since the class IC antiarrhythmic agents have been prescribed using proper dose rates.[7] Finally, the occurrence of syncope, cardiac arrest or sudden cardiac death which is undocumented as to its mechanism should be considered a proarrhythmic event when it occurs early on after a potentially proarrhythmic drug has been prescribed. Obviously, such an event cannot be distinguished from inefficacy or a change in the natural history of the patient's underlying condition but nevertheless we recommend that such phenomena arbitrarily be classified as proarrhythmic events unless they have occurred after one month of the same daily dose of the drug.

TABLE 1

DEFINITION OF PROARRHYTHMIA

1. New onset of:

   a. Ventricular premature complexes (VPCs) >5 per hour
   b. Nonsustained ventricular tachycardia (defined as less than 30 seconds without hemodynamic consequence
   c. Sustained ventricular tachycardia (defined as ≥30 seconds or requiring termination because of hemodynamic response)
   d. Torsades de pointes or polymorphic ventricular tachycardia
   e. Ventricular flutter/fibrillation
   f. Supraventricular tachycardia
   g. Atrial fibrillation or atrial flutter

2. Change in the Frequency of a Previously Documented Ventricular Arrhythmia:

   a. Increase in frequency of VPCs:

Mean VPCs/hour At Baseline	Increase Required for Proarrhythmia
10-50	10X
51-100	5X
101-300	4X
>300	3X

   b. A 10-fold or greater increase in the mean hourly frequency of nonsustained ventricular tachycardia beats

3. A significantly more difficult cardioversion or termination of ventricular tachycardia or ventricular flutter/fibrillation as defined by the treating physician.

4. Occurrence (within 1 month) of syncope, cardiac arrest or sudden cardiac death in which the mechanism is unknown.

LEVEL OF CERTAINTY AND CLINICAL RELEVANCE OF PROARRHYTHMIA

The level of certainty that the proarrhythmia was due to the drug is related to the reproducability of the observation. Obviously, rechallenging the patient after reestablishing a baseline provides the most objective means of confirming a proarrhythmic response. Such a rechallenge may be difficult to accept when the potential proarrhythmic response was life-threatening but in the absence of a rechallenge the level of certainty may only be ascribed as probable.

The clinical relevance of the proarrhythmic response is an extremely important differentiating feature of this phenomena. We have suggested[7] that proarrhythmic responses which are primary be assigned to categories termed: those that cause "death", those that are "serious", and "other". Table 2 details the segregation of the definitions used in Table 1 into these 3 categories.

TABLE 2
CLINICAL IMPORTANCE OF PROARRHYTHMIA

The proarrhythmic event may cause:

Death

Any proarrhythmic event resulting in death

Serious

Items from Table 1:
1c, 1d, 1e, 1f, 1g if hemodynamically significant
3
4

Other

Items from Table 1:
1a, 1b, 1c, 1d, 1f, 1g if not hemodynamically significant
2a
2b

Important insights can be gained from such a classification. For example, Table 3 details the proarrhythmic incidence from the antiarrhythmic drug flecainide in which all proarrhythmic events are categorized into those that caused "death", "serious" or "other". Detailing the ventricular proarrhythmic responses by ventricular arrhythmia class of the patient being treated also provided important insights into the frequency of proarrhythmia. As can be seen from Table 3, the overall proarrhythmic incidence of 7% would suggest that flecainide is similar to the degree of proarrhythmia observed from other antiarrhythmic drugs.[1]

TABLE 3

PROARRHYTHMIA RATES ON FLECAINIDE DIFFERENTIATED BY TYPE OF RESPONSE

	VENTRICULAR ARRHYTHMIA CLASS			
	BENIGN	POTENTIALLY LETHAL	LETHAL	ALL PATIENTS
	N=470	N=469	N=391	N=1330
ALL PROARRHYTHMIC EVENTS	8 (2%)	18 (4%)	64 (16%)	90 (7%)
"DEATHS"	0 (0%)	1 (0.2%)	12 (3%)	13 (1%)
HIGH DOSE RATE	--	--	10/100 (10%)	--
PROPER DOSE RATE	--	--	1/198 (0.5%)	--
"SERIOUS"	0 (20%)	4 (0.9%)	26 (7%)	30 (2%)
"OTHER"	8 (2%)	13 (3%)	26 (7%)	47 (4%)

However, the prevalence of "death" and "serious" proarrhythmic events occurred more commonly in patients with lethal or malignant ventricular arrhythmias. Patients with benign or potentially lethal ventricular arrhythmias[8] appeared to have a far less rate of proarrhythmia and probably less than that seen for other antiarrhythmic drugs.[9] The inappropriate use of a high dose rate of flecainide produced proarrhythmic death in patients with lethal ventricular arrhythmias with an extremely high incidence of 10% whereas when a proper dose rate was used the death rate dropped by 1/20 to 0.5%.[2,7]

The prevalence of "other" proarrhythmic events was not so clearly related to the patient's type of ventricular arrhythmia at baseline suggesting that this form of proarrhythmia may have little clinical relevance.

SUMMARY

Substantial progress has been made in the last few years in describing a definition for proarrhythmia and detailing the risk factors associated with its occurrence. Models to determine the cellular mechanisms responsible for proarrhythmia will be required before more definitive judgments concerning proarrhythmia will evolve. At present, we recommend that proarrhythmic responses to drugs be carefully considered in protocol designs and that full descriptions of each event be provided. We hope that the definitions and concepts suggested in this manuscript can be used as a foundation for future developments.

REFERENCES

1. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB: Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982; 65:886-894.

2. Morganroth J and Horowitz LN: Flecainide:Its Proarrhythmic Effect and Expected Changes on the Surface Electrocardiogram. Am J Cardiol 1984;53:89B-94B.

3. Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB: Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 1978;58:408.

4. Horowitz LN, Zipes DP, Bigger JT, Campbell RWF, Morganroth J, Podrid PJ, Rosen MR, Woosley RL: Proarrhythmia, arrhythmogenesis or aggravation of arrhythmia - A status report - 1986. Am J Cardiol (in press).

5. Kostis JB, McCrone K, Moreya AE, et al: Premature ventricular complexes in the absence of identifiable heart disease. Circulation 1981;63:1351-1356.

6. Morganroth J: Application of a Frequency Definition of Ventricular Proarrhythmia. Am J Cardiol 1986 (in press).

7. Morganroth J, Anderson JL, Gentzkow GD: Classification by Type of Ventricular Arrhythmia Predicts Frequency of Adverse Cardiac Events from Flecainide. J Am Coll Cardiol 1986;8:607-615.

8. Morganroth J: Premature Ventricular Complexes:Diagnosis and Indications for Therapy. JAMA 1984;252:673-676.

9. Horowitz LN and Morganroth J: Second Generation Antiarrhythmic Agents: Have We Reached Antiarrhythmic Nirvana? J Am Coll Cardiol 1986 (in press).

9

Criteria for Proarrhythmia in Patients with Congestive Heart Failure: Use of Electrophysiologic Testing

Leonard N. Horowitz, M.D.

The mortality of patients with severe left ventricular dysfunction and congestive heart failure ranges from 25 to 50%. Almost half of the deaths of patients with heart failure are sudden, presumably due to malignant ventricular arrhythmias (1-5). Moreover, in such patients asymptomatic or only minimally symptomatic ventricular arrhythmias are common (1-5). Frequent and complex ventricular arrhythmias which occur in conjunction with depressed left ventricular function are associated with an increased risk of malignant ventricular tachyarrhythmias and it would seem logical that suppression of these asymptomatic arrhythmias would improve the prognosis of patients with heart failure. This, however, has yet to be validated. In fact, little data have been presented to support the notion that suppression of ventricular arrhythmias will lead to a reduction in the sudden death rate in these patients.

The controversy as to whether antiarrhythmic therapy reduces mortality aside, other concerns have been raised regarding the use of antiarrhythmic therapy in patients with congestive heart failure. Antiarrhythmic drugs can depress left ventricular function further and worsen congestive heart failure and in patients with left ventricular dysfunction the metabolism and elimination of these agents may be less predictable. Another significant concern about antiarrhythmic therapy has been raised since the recognition that antiarrhythmic drugs may provoke or worsen ventricular arrhythmias rather than suppress them. The phenomenon, proarrhythmia, has been observed to be more common in patients with left ventricular dysfunction and/or congestive heart failure in a number of studies (6-8). Therefore, antiarrhythmic drugs may prove to be particularly dangerous in one population of patients with the greatest need for them.

Definitions of proarrhythmia and methods for detecting it are becoming available. Although agreement in this field has been minimal, data upon which objective statements can be made is in the offing.

Definition of proarrhythmia

It has been recognized for sometime that antiarrhythmic drugs could parodoxically produce arrhythmias. In the 1940s, paroxysmal ventricular fibrillation resulting from antiarrhythmic therapy was

emphasized (9) and in the 1960s this was popularized as "quinidine syncope" (10). Since then, drug-related provocation and worsening of arrhythmias have been well recognized as a potential toxicity of all anti-arrhythmic drugs (11-15). The utility of non-invasive techniques for identifying and defining arrhythmias has been discussed in the previous chapter. In this chapter I will address the use of invasive electrophysiologic testing to identify and evaluate the proarrhythmic potential of antiarrhythmic agents in this population of patients.

Although the term proarrhythmia includes both bradyarrhythmias as well as supraventricular and ventricular tachyarrhythmias, I will focus on ventricular tachyarrhythmias as a manifestation of proarrhythmia in this discussion. Certain criteria for the development of proarrhythmia have been generally accepted. The development of torsade de pointes with QT prolongation and the onset of uniform morphology sustained ventricular tachycardia coincident with antiarrhythmic drug administration are examples of such criteria. Other criteria have been less well accepted and require verification with objective data.

In addition to simply enumerating criteria for drug-induced worsening of arrhythmias, some attempts should be made to state the clinical relevance of the observed effect. Moreover it is important to indicate whether the ocurrence of the proarrhythmic response is

due simply to the presence of the antiarrhythmic drug or whether concomitant factors such as electrolyte disturbances or other intercurrent conditions are necessary.

Use of electrophysiologic testing to identify the proarrhythmic potential of antiarrhythmic drugs

The utility of electrophysiologic testing to identify effective antiarrhythmic regimens in patients with malignant ventricular arrhythmia is well established (16-19). It has more recently been suggested that such studies may also be useful in identifying proarrhythmic responses to antiarrhythmic agents. An early study in this regard by Ruskin et al (20) suggested that the potential for malignant ventricular arrhythmia could be predicted by electrophysiologic studies. In a small group of patients who had suffered out of hospital cardiac arrest while receiving an antiarrhythmic drug, these investigators were not able to induce the ventricular tachyarrhythmia during electrophysiologic testing when the patients were receiving no antiarrhythmic drugs. However, in four patients ventricular tachycardia was inducible when they were placed on the antiarrhythmic medication which they were receiving at the time of their spontaneous cardiac arrest. These data have been used by some to suggest that electrophysiologic testing may be useful in predicting the proarrhythmic potential

of antiarrhythmic regimens. No large scale test of this hypothesis, however, has been performed to date.

Other investigators (21-23) have reported that sustained ventricular tachycardia can be induced following antiarrhythmic drug administration in certain patients in whom only non-sustained ventricular tachycardia could be induced prior to drug administration. In these studies, 5 to 15% of patients with inducible non-sustained ventricular tachycardia had sustained ventricular tachycardia induced while receiving an antiarrhythmic regimen. In many patients in whom this phenomenon is demonstrated, the electrophysiologic parameters measured suggest that drugs alter conduction velocity in depressed tissue enhancing the potential for the development of self-sustaining re-entrant circuits. Whether such observations indicate that the drugs would produce this same response spontaneously is yet to be validated.

Antiarrhythmic drugs have been reported to alter ventricular tachycardias which had been hemodynamically stable and cause them to result in marked hypotension and syncope. Such a response has been noted in 2 to 7% of patients undergoing electrophysiologic study and drug testing for ventricular tachycardia (22, 23). Typically cardioversion is required for termination of tachycardia in such patients. The worsening of symptoms and the requirement for cardioversion may reflect the impact of antiarrhythmic regimen not only

on the electrophysiologic properties of the ventricle but also the mechanical properties. Negative inotropism may play a significant role in this effect. Previous studies have also suggested that a reduction in the number of extrastimuli required for initiation of ventricular tachycardia or ventricular fibrillation during electrophysiologic study might be an indication of a proarrhythmic response. Poser and co-workers subclassified this type of response into definite proarrhythmia when the number of extrastimuli was reduced by two and possible proarrhythmia when the number of extrastimuli was reduced by one. The incidence of this type of proarrhythmia ranges from 6 to 20% in various studies (22-24). Obviously this type of proarrhythmia is very dependent upon the reproducibility of the mode of induction of the arrhythmia in the baseline state. Questions about reproducibility, particularly with regard to the number of extrastimuli have been raised and validation of this criteria for proarrhythmia is necessary before it can be accepted.

Proarrhythmic response during electrophysiologic testing

In a study of 160 consecutive patients with ventricular tachyarrhythmias associated with coronary artery disease, 432 trials of antiarrhythmic regimens were evaluated by electrophysiologic techniques for

proarrhythmic effects. The mean left ventricular ejection fraction in this group of patients was 30%. The arrhythmia initiated in the baseline state was ventricular tachycardia in 121 patients, ventricular fibrillation in 16 and symptomatic non-sustained ventricular tachycardia in 23. Overall a proarrhythmic response was observed in 68/432 (16%) drug trials. At least one proarrhythmic was observed in 51/160 (32%) patients (23).

In 23 patients in whom only non-sustained ventricular tachycardia was inducible during a baseline study, 59 antiarrhythmic regimens were evaluated. In 10/59 (17%) of these studies sustained ventricular tachycardia or ventricular fibrillation was induced by programmed electrical stimulation. This effect was noted in 6 of the 23 patients.

Conversion of a previously stable ventricular tachycardia to one which required cardioversion either because the tachycardia could not be terminated by programmed stimulation or produced syncope prior to conversion by programmed electrical stimulation occurred in 15/325 (5%) studies. Typically cardioversion was required because the ventricular tachycardia had a shorter cycle length during drug administration than during the baseline state, however, hemodynamic deterioration was noted during some tachycardias in which the cycle length was prolonged. Presumably in these latter patients the requirement for

cardioversion was the result of both electrophysiologic and hemodynamic alterations caused by drugs.

In 43/373 (12%) studies in which a sustained ventricular tachyarrhythmia was initated in the baseline state, fewer extrastimuli were required during a drug study (24).

Although electrophysiologic testing was not the usual evaluation method during which spontaneous development of ventricular tachycardia is observed, during 3 drug trials of intravenous regimens, spontaneous ventricular tachycardia occurred without the use of programmed stimulation and was considered a proarrhythmic response.

In this study of 160 patients with coronary artery disease and malignant ventricular arrhythmia, there was no significant difference in the incidence of proarrhythmic responses between various agents and combination regimens. There has been some suggestion that the incidence of proarrhythmia may be higher with certain agents (21) however studies in larger patient groups are required before this can be ascertained with certainty.

Limitations in the use of electrophysiologic studies to define proarrhythmic responses

The major limitation in using electrophysiologic testing to identify proarrhythmic responses to antiarrhythmic regimens at present is the unknown

relationship between the observed effects during electrophysiologic testing and spontaneous development of drug related proarrhythmia. In addition, the reproducibility of the proarrhythmic responses during electrophysiologic testing has not been studied.

During electrophysiologic testing for selection of effective antiarrhythmic regimen, reproducible initiation of the clinical arrhythmia and the reproducibility of the therapeutic effect are required (16-19). The studies which have been reported to date investigating proarrhythmia as defined in the electrophysiology laboratory have not addressed reproducibility. The second limitation with regard to electrophysiology definition of proarrhythmia is more problematic. Whether we will be able to evaluate the correlation between observations made in the electrophysiology laboratory and spontaneous proarrhythmia is uncertain. For certain criteria, particularly the reduction in a number of extrastimuli needed for induction of arrhythmia, clinical correlation may be obtained, however, in more serious forms of proarrhythmia particularly when ventricular tachycardia is worsened with respect to its hemodynamic consequences, the ethics of such of a prospective correlation can be questioned.

Conclusions

Proarrhythmia caused by antiarrhythmic drugs

particularly in patients with reduced left ventricular function and congestive heart failure is an important and clinically significant issue. Ideally we could identify prospectively whether antiarrhythmic regimens in this patient population would worsen or provoke ventricular arrhythmia. Although both non-invasive and invasive techniques have been applied to this question, the clinical significance of observations with either technique are not fully validated at present. Several definitions to proarrhythmia response have been suggested and further study will be required before they are established as a useful criteria in the management of patients with ventricular arrhythmias and reduced left ventricular function.

References

1. Franciosa JA, Wilen M, Ziesche, et al: Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1983;51:831-836.

2. Wilson JR, Schwartz JS, Sutton M, et al: Prognosis in severe heart failure: Relation to hemodynamic measurements and ventricular ectopic activity. J Am Coll Cardiol 1983;2:403-410.

3. Unverferth DV, Magorien RD, Moeschberger ML, et Factors influencing the one-year mortality of dilated cardiomyopathy. Am J Cariol 1984;54:147-152.

4. Fuster V. Gersh BJ, Giuliani ER, et al: The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981;47:525-531.

5. Califf RM, Burks JM, Behar VS, et al: Relationship among ventricular arrhythmias, coronary artery disease and angiographic and electrocardiographic indicators of myocardial fibrosis. Circulation 1978;57:725-732.

6. Morganroth J, Anderson JL, Gentzkow GD: Classification by type of ventricular arrhythmia predicts frequency of adverse cardiac events from flecainide. J Am Coll Cardiol 1986;8:607-615

7. Morganroth J: Risk factors for the development of proarrhythmic events. Am J Cardiol (in press).

8. Rae AP, Greenspan AM, Spielman SR, Horowitz LN: Proarrhythmia during electorphysiologic studies. (abstr) Brit Heart J (in press).

9. Schwartz SP, Hallinger L, Imperialli A: Transient ventricular fibrillation. IV. The effects of procainanide on patients with transient ventricular fibrillation during established auriculo-ventricular dissociation. Circulation 1952;6:193-200.

10. Selzer A, Wray HW: Quinidine syncope: Paroxysmal ventricular fibrillation occurring during treating of atrial arrhythmia.

Circulation 1964;30:17-26.

11. Cocco G, Strozzi C, Chu D, Pansini R: Torsade de pointes as a manifestation of mexiletine toxicity. Am Heart J 1980;100:878-880.

12. Strasberg B. Sclarovsky S, Erdberg A, Duffy CE, Lam W, Swiryn S, Agmon J, Rosen KM: Procainamide-induced polymorphous ventricular tachycardia. Am J Cardiol 1981;47:1309-1314.

13. Winkle RA, Mason JW, Griffin JC, Ross D: Malignant ventricular tachycardia associated with the use of encainide. Am Heart J 1981;102:857-864.

14. Velebit V, Podrid P, Lown B, Cohen BH, Graboys TB: Aggravation and provocation of ventricular arrhythmias by antiarrhythmic drugs. Circulation 1982;65:886-894.

15. Sclarovsky S, Lewin RF, Kracoff O, Strasberg B, Arditta A, Agmon J: Amiodarone-induced polymorphous ventricular tachycardia. Am Heart J 1983;105:6-12.

16. Mason JW, Winkle RA: Electrode-catheter arrhythmia induction in the selection and assessment of antiarrhythmic drug therapy for recurrent ventricular tachycardia. Circulation 1978;58:971-985.

17. Horowitz LN, Josephson ME, Farshidi A, Spielman SR, Michelson EL, Greenspan AM: Recurrent sustained ventricular tachycardia 3. Role of the

elctrophysiologic study in the selection of antiarrhythmic regimens. Circulation 1978;58:986-997.

18. Swerdlow CD, Winkle RA, Mason JW: Determinants of survival in patients with ventricular tachyarrhythmia. N Engl J Med 1983;308:1436-1442.

19. Mason JW, Winkle RA: Accuracy of the ventricular tachycardia-induction study for predicting long-term efficacy and inefficacy of antiarrhythmic drugs. N Engl J Med 1980;303:1073-1077.

20. Ruskin JH, McGovern B, Garan H, DiMarco JP, Kelly E: Antiarrhythmic drugs: A possible cause of out-of-hospital cardiac arrest. N Engl J Med 1983;309:1302-1306.

21. Rinkenberger RL, Prystowsky EN, Jackman WM, Naccarelli GV, Heger JJ, Zipes DP: Drug conversion of nonsustained ventricular tachycardia to sustained ventricular tachycardia during serial electrophysiologic studies: Identification of drugs that exacerbate tachycardia and potential mechanisms. Am Heart J 1982;103:177-184.

22. Torres V, Flowers D, Somberg JC: The arrhythmogenicity of antiarrhythmic agents. Am Heart J 1985;109:1090-1097.

23. Rae AP, Greenspan AM, Spielman SR, Sokoloff NM,

Webb CR, Kay HR, Horowitz LN: Antiarrhythmic drug efficacy for ventricular tachyarrhythmias associated with coronary artery disease as assessed by electrophysiologic studies. Am J Cardiol 1985;55:1494-1499.

24. Poser RF, Podrid PJ, Lombardi F, Lown B: Aggravation of arrhythmia induced with antiarrhythmic drugs during electrophysiologic testing. Am Heart J 1985;110:9-16.

DISCUSSION-2

Dr. Moore: Dr. Ehrreich, what is the best animal model that you would advise a pharmaceutical concern to utilize to evaluate a potential new drug against congestive heart failure?

Dr. Ehrreich: Wearing the old FDA hat, that is a very difficult question, because I mentioned in my talk that there are at least three factors involved. There is the relevance of the model, the cost and the ease with which the model can be used. Those factors are over-riding and in some cases the cost is very appropriately placed as a stepping stone to which model you are going to use. At one time, we were going to use conscious dogs to study myocardial infarction and it turned out that it cost$ 250-300 per dog to use that as a primary screen. The total cost to the company would be like $10,000 per month and they said no. Obviously that is one of the factors. One of the models that I mentioned, the rat with heart failure may very well turn out to be a very interesting model to use. Rats are relatively cheap to keep, but are not easy to breed but it can be done. They are not only easy to keep, but easy to use, and in the studies I have reviewed, the hemodynamics of heart failure are easy to study as well: To answer the question off the top of my head, I would suggest probably the rat is a good model and there isn't much to know about it yet, but my suggestion would be that at the present time.

Dr. Moore: I would like to ask Dr. Lipicky, what would the FDA accept, what would you like to see?

Dr. Lipicky: I think if I were looking for an inotrope, I would probably use cat papillary muscle. If I was looking for a vasodilator, I would probably use some vascular strip. If I was looking for some other thing that presumably I know would alter some physiological function, I would use some simple *in vitro* model. What hypothesis would one presumably be testing by having an animal model of the disease? That is not clear to me at all.

Dr. Ehrreich: What Ray is pointing out in terms of papillary muscle and so forth is perfectly correct. However, as a primary screen, unless you are looking as he said for a specific mode of action of mechanism of action, a drug company doesn't do that. If you are looking for an ACE inhibitor, Squibb was very successful in designing very nice *in vitro* studies to look at ACE inhibitors and you could test 10 or 15 compounds at a time and come up with the best ACE inhibitor. One of the things, if you don't know what the mode of action will be of the eventual drug you find, and you are looking at the whole organismic model of heart failure, presumably, you are going to come up with a drug that has a mode of action similar to what Ray mentioned. It might be an inotrope, it might be a vasodilator, it might be whatever, and the point of the primary screen is to find multiple modes of action in the cheapest, fastest way. I think that is really something that has to be brought out and some of these other models turn out to be secondary tests, when you think you know what the mode of action is of the drug that you did find in the primary model.

Dr. Moore: Dr. Temple, do you have any comments on what you would like to see in pre-clinical data.

Dr. Temple: No in a fairly real sense, our preclinical pharmacology requirements are very flexible to say the least. We worry a lot about toxicology, but if on the whole, the sponsor thinks he has enough rationale to proceed, we are usually inclined to let him do so. I can't think of very many situations outside of oncology perhaps where this comes up, where we would say, oh, no, you haven't done enough animal models, go away. I wouldn't rule it out, but it would be quite unusual. The purpose of using the whole animal as opposed to a papillary strip, is that it is an integrated response. You learn not only that it makes the papillary muscle contract better, but that somehow the overall effect is favorable as well. It covers a whole lot of things, and perhaps we can avoid misleading you. Certainly if you were screening millions of compounds, the way to do it is in the simplest, cheapest preparation. I assume that is how it is done.

Dr. Moore: So it depends on whether you are screening or are looking for a mechanism and have already identified something that is effective for congestive heart failure, what would you like to see in preclinical studies that would suggest to you that you would be happy, you would be excited, you would be interested in trying this in man.

Dr. Packer: Are we talking about its potential proarrhythmic effects or are we talking about its circulatory effects.

Dr. Moore: I am talking about it being an effective agent to improve exercise or whatever we want to improve. I mean do we want to improve so they can walk and talk and urinate, but what do you want to know.

Dr. Packer: I think again, it is similar to what Ray said, it depends on what you want. If you are developing a positive inotrope, you would like to know it is a positive inotrope. It is a self-fulfilling prophecy. If you are developing vasodilators, you would like to know it had vasodilator capacity. Except for that, the importance of preclinical guides you to a potential mechanism of action and certain mechanisms of action are presumably at least on historical basis a little bit more successful than other mechanisms of action. If the trial is on alpha blockers for instance in heart failure and had not been very encouraging either in terms of exercise capacity or in terms of survival then if you develop another drug and it vasodilates by an alpha blocking mechanism I am not certain I would be all that excited about that I think the usefulness of preclinical is that it permits you to do a lot of things you could not do in man in terms of a mechanism of vasodilatation or inotropy.

Dr. Morganroth: I guess that if the drug were proposed to be an inotrope, lets take one example, and I saw that in the preclinical model it increased measures of left ventricular systolic function as dp/dt, cardiac index and the like, but did it at the expense of heart rate without associated ischemia, so that in models, the heart rate went up more than the cardiac index for example, I would be a little concerned about what the ultimate benefit would be. I think the animal models to me are more important for toxicology.

Dr. Moore: You wouldn't accept some of the things we are accepting in man, like quality of life. I mean if the cats purr

longer, and, with exercise tolerance, you make a field trial champ out of a beagle, that type of thing you wouldn't be satisfied with?
Dr. Lipicky: I don't know why we don't. As a regulatory body we look for a whole set of data before going for the first time in man. One clear thing which I think you are alluding to is what kind of safety margin might you expect from this drug when you are going first time in man. It would be nice to know what the dose response looked like in animals with a variety of things so that you have some feeling about how you might be able to increment doses in man. It would be nice to know something about the mechanism of action of the drug so that in fact, if you got into trouble and actually had this supported by data from the early investigative stuff in the laboratory, if you got into trouble, what might you do in order to get out of trouble. Clearly if you don't know the mechanism and you don't know what the adverse phenomenonological effects are and how they relate to dose, then you have no idea whether raising calcium or changing the pH or giving this or that can help you get out of trouble. It seems to me you are really standing rather alone when you are giving those first few doses in man.
Dr. Moore: Dr. Temple, I know that you had some comments on mechanisms and how important they are.
Dr. Temple: I think everything Ray said is perfectly true. We look at all those things at the toxicologic level and I guess it is true. I don't know whether you learn more about the potential toxicity of the drug from whether we have taken the opportunity to learn more about potential toxicity of the drug from some of these models. I think on the whole we probably have not. I don't know whether they are useful that way. Certainly the example that Joel gives, an inotrope that had a profound increase in tachycardia, you would certainly want to watch for that and it would be helpful to know it. I don't think there is any doubt about that. You certainly want to know what the basic properties of the drug are. Whether you learn those from these models or not, I am not sure, but you want to know if a drug has any cholinergic properties and things like that. It should be characterized reasonably well in the usual screens and they usually are. The thing that I am saying is we have not typically made stringent demands that it be effective in some particular model. It may be that we don't see drugs that aren't. I can't remember an antihypertensive drug that hasn't been run through a spontaneously hypertensive rat or some similar model. It is just done routinely, I presume that is because companies don't want to bother with things that don't work in any reasonable model on waste of money grounds.
Dr. Ehrreich: One comment. I remember seeing one time a drug that came through for review that did nothing but inhibit an enzyme. I am not talking about ACE enzyme. I am talking about another one, in which the only animal data that existed was the fact that it inhibited this enzyme in the pathway for synthesis of noradrenaline and the company then went ahead and tested various human models to see what value it had. It turned out that it really didn't have any value, but the point is that the agency doesn't request or require a model that the drug works in that is clinically relevant before you

can go into clinical testing. It is the people at the drug company that require that.

Dr. Garvey: I thought I heard in presentations that preceded the inception of the panel discussion that sudden death was a relatively common cause of exodus in patients with congestive heart failure, presumably related to lethal ventricular arrhythmias and I am curious as to whether the panel might like to comment on the potential utility of monitoring of effects on potentially lethal ventricular arrhythmias of drugs as a possible effectiveness parameter when you are working up an agent for congestive heart failure. We have had so much indication that we don't have a good end point. Could somebody address that?

Dr. Morganroth: That is an interesting idea. We don't know that for an antiarrhythmic drug effect that it is useful to the person receiving the antiarrhythmic drug to have their potentially lethal ventricular arrhythmias eliminated. I believe that Dr. Fisher said that was the cosmetic effect of the Holter monitor and that the Cardio-Renal Advisory Committee believes that in the arrhythmia population one has to demonstrate a benefit on quality of life or symptoms if sudden death prevention has not been shown.

Dr. Garvey: I was thinking of something else. I was curious about the correlation between the type and frequency or prevalence of ventricular arrhythmia and the risk of sudden death in a population with congestive heart failure and whether we know anything about the effects of the usual interventions in congestive heart failure on these potentially lethal arrhythmias.

Dr. Morganroth: You have hit a controversy. I will state my position first and then the counter position will be given. Some of us believe that sudden cardiac death occurs in about 50% of heart failure patients as the mode of exodus and that ventricular arrhythmias occur in anywhere from 50-80% of these patients. Complex ventricular arrhythmias defined as repetitive forms such as non-sustained ventricular tachycardia occur on the average in about 75% of these patients. The Holter monitoring studies in patients with chronic heart disease that have been reported in the past in patients who fortuitously were wearing a Holter monitor at the time they had their demise, in 80% of the cases, that a ventricular tachyarrhythmia leading to fatal ventricular fibrillation was present, documenting your suggestion that most of these sudden deaths, but not all were probably arrhythmic and due to a ventricular tachyarrhythmia. The question is, what is the relationship between the complex ventricular arrhythmias which are common and the sudden cardiac deaths which I guess is also common, being 50% of the mode of exodus. In studies in the post-myocardial infarction population particularly, as possibly in the heart failure population, there is a clear independent relationship between LV function and ventricular arrhythmias on sudden death mortality. Whether suppression of those arrhythmias will prevent sudden death is unknown because no one has tested it properly.

Dr. Garvey: I want to hear the other side of this. Does conventional therapy, or even unconventional therapy for congestive heart failure leaving out antiarrhythmics results in any putatively beneficial change in the frequency etc. of these events?

Dr. Morganroth: Not with digoxin where it has been looked at, although there is some controversy there. The Lown group believes that it does, but most others have less certainty of that. There is some suggestion that ACE inhibitors may.

Dr. Packer: I think one point that needs to be made, which is an extremely difficult point to address: it is relatively easy in the patient population of ischemic heart disease after a myocardial infarction that does not have congestive heart failure to develop a satisfactory definition of sudden death which is most likely attributable or can be attributed to a ventricular arrhythmia. It is very hard to define sudden death in this patient population. If you think about it, all death is sudden. One moment the patient is there, and the next moment, the patient is not. The problem is that in patients with heart failure who are progressively deteriorating over time, it is very hard to distinguish death from heart failure to death from arrhythmias. It is very difficult. If you look at clinical histories, as in the mortality of the BHAT trial, it is extremely difficult at times, if not in the majority of cases to distinguish a sudden presumably arrhythmic demise, from a death secondary to congestive heart failure. If there is such a link and if patients are dying of their arrhythmias, we do not know if these arrhythmias are a marker of the severity of the underlying disease or are a primarily pathogenetic factor that leads to premature death. We do not know that and therefore we don't know if treating them kills the messenger without taking care of the underlying disease. That is the key thing. Most of the drugs that we have for the treatment of congestive heart failure have not been evaluated well in this regard. There is very little long term data on digitalis in terms of arrhythmias, although we suspect that if anything, it may be proarrhythmic. Diuretics we suspect may be proarrhythmic because of their metabolic consequences: potassium depletion and an increase in neural hormones. We fear the consequences of drugs that increase cyclic AMP such as the catecholamines. The only drug class that we know of that potentially has an ameliorative effect on the arrhythmias are the converting enzyme inhibitors. There are now three double blind placebo controlled trials short term with converting enzyme inhibitors but that may be mediated by their metabolic effects, because they raise potassium and they decrease catecholamines and not by their hemodynamic effects. It is a wide open area. We don't know.

Dr. Siegl: I have a question related to how the discussion began, before it got to arrhythmias. The criteria of a compound being interesting in heart failure as discussed by the speakers this morning would be one that changed the progression of the disease or prevented mortality. That is difficult to do in animal models, but can be done now with some of the genetic models as well as healed myocardial infarction models. None of the speakers have talked about criteria such as that as being interesting. They have only talked about acute effects so I wonder if we could discuss compounds that might change the course of the disease, without an acute hemodynamic effect. How might those be viewed? Also, clinical

trials are going to be more difficult because it is going to require a longer period of time.

Dr. Temple: But they would be interesting.

Dr. Moore: Difficult and expensive.

Dr. Temple: It is hard to know what to say. I mean if someone had some imaginative intervention in one of these models that kind of made the whole thing go away, I imagine that people would get interested and excited about it.

Dr. Siegl: Dr. Sonnenblick pointed out that to prevent the cells from dying would be a case of something that might be effective.

Dr. Temple: I guess the question always is how much those things tell you. I remember from years ago, an enormous literature from some early agents that turn out in retrospect to be calcium antagonists, about how they seem to increase the total cardiac vascular mass and all kinds of interesting things, but it isn't clear that those have ever worked out in man later and its hard to say why. It may just be that it is too hard to study and that animals are simpler because they only have one lesion. On the other hand, some of them do. I guess you would have to say that the early suggestions about what beta blockers do have been reasonably well confirmed in man, so animal models often do tell you things.

Dr. Sonnenblick: I think there really is some very specific data. I mean very specifically in the one animal model that is quite predictable is the serian hamster that develops a cardiomyopathy in a very predictive fashion and Stu presented some of that data. Clearly, you can demonstrate that you can abort the development of a cardiomyopathy, you can stop it in mid course, while you give the drug, you keep the myopathy from occurring and when you stop the drug, the myopathy then recurs and goes on. That is the only instance that I know in which it has been shown that a very specific drug intervention prevents the disease, prevents the pathology and ameliorates the failure. That has been well established by three different groups.

Dr. Lipicky: Is that a drug you can name?

Dr. Sonnenblick: Verapamil. I think the reason it hasn't been tested is it doesn't have a patent anymore, and it is very expensive to test a drug like that in a clinical setting and it really is one of the challenges. What do you do with orphan drugs? Dopamine had an awful hard time getting studied and approved because it was an orphan drug, and that is a problem. That is one specific example. I think the whole issue of beta blockers is another that I think can be tested in that same way. Whether it can be tested in animal models I am not so certain. There is one other issue about animal models and that is there is a species dependency to inotropic responses. Catecholamines have virtually no response in rats at all. So you have to pick your shots. I don't know of any discrepancy between what the dog and the cat and what man does, but certainly in the other species, I think that this was alluded to. You can get discrepancies there. That is one thing that might be tested in man. The only problem is how do you identify somebody with the disease early enough to prevent the process and progression?

Dr. Moore: Yourcomment about differences in species is very interesting Ed, because of course digitalis is effective in man, cat and dog, but you don't get digitalis toxicity in a rat. They love the stuff.

Dr. Cohn: This issue about early intervention to influence the mechanism I think is a terribly critical issue. I think all of us who work in the field of heart failure are somewhat despondent about intervening in Class IV and Class III failure because we recognize the total benefits are modest in that situation. The dog model that we use, which Stu did not mention, is one in which heart damage leads to progressive failure over a three or four month period of time and that model is nice because it has all the earmarks of human heart failure at the 3-4 month stage. The sympathetic nervous system is activated, plasma catechols are up, there are high filling pressures, low outputs, dilated hearts and one could use that kind of model. I think to look at natural history of progressive ventricular dysfunction because what you do is damage the left ventricle initially and you create a lesion which is then thereafter stable and the rest of the heart gradually dilates and decompensates and the animal becomes progressively impaired as a result of some process set into motion by the initial left ventricular damage. I happen to be an advocate of the hypothesis of the big bang theory, that is you get acute damage to the heart and the process then becomes self-perpetuating. Ed Sonnenblick is probably more of an advocate of the continuing insult process. I think that a lot of progression occurs without necessarily there being any further insult to the myocardium externally, but rather the internal processes which become activated and chronic models in awake dogs such as the one that we use, I think provide an opportunity to evaluate that in a way that the human syndrome really does not provide. The issue of arrhythmias came up and our view of that from looking in the VHEFT data and some other data is that the ventricular tachyarrhythmias are almost ubiquitous in heart failure. Probably even higher than 50-80% when you look at rather severe patients and they are indeed an independent marker for mortality above and beyond ejection fraction of the left ventricular function. The problem is that they are a marker for mortality both for sudden death and for pump failure, so that although you would like it to be that the arrhythmia is a marker for sudden death and the ejection is a marker for pump failure, the fact is that they are both markers for both kinds of death and there have been some trials which have suggested that if you can eliminate the arrhythmias you may actually reduce the incidence of sudden death in such patients, but you increase the risk of pump failure death and you don't change the mortality at all. I think we are dealing with a multifactorial system and the arrhythmias just tell you that the heart is bad and the patient isn't going to survive terribly long.

Dr. Morganroth: That actually addresses Dr. Garvey's question doesn't it? He was asking from the data you just presented, the question could one use as a marker for a "heart failure" drug as an efficacy parameter, a reduction in ventricular arrhythmias. Would you buy that as an another independent marker, whether they reduce VPC's or non-sustained VT.

Dr. Lipicky: Sure.
Dr. Cohn: We don't know the therapeutic effect is accompanied by a beneficial effect on survival. We have the baseline prognostic value of these things, but we don't have the role of the interventions yet in influencing.
Dr. Lipicky: Just coming back to the animal model business and what its purpose would be. Indeed one could use the animal model to look at whether or not drug X will interfere with the natural history of the disease in that animal model, the question is, what purpose that information would be put to. For example, if drug X did not alter the natural history of the disease in the animal model, would that mean that drug X would then never be a candidate for a trial in man or would one indeed be attempting to identify drugs in the animal model system that behave differently from the point of view of fixing the animal model and then in fact plan clinical trials that would validate the animal model to determine whether they had predictive value. That is not clear to me exactly what the purpose of the model would be. Not that it isn't of great interest.
Dr. Cody: I would like address this to Joel to the issue of proarrhythmic effect, defining it and then trying to analyze it in terms of some special problems that may be apparent in the heart failure population and this follows up on Jay Cohn's comments to some degree. Just looking at some of the definitions that you put up Joel, for instance if an arrhythmia is not present in the baseline, and you create it, that is a proarrhythmic effect. A large number of our patients also have a high degree of ectopy on the baseline state and that is most people's experience so in that sense you are not creating the arrhythmia because it is already there. Some of the other ways that you could demonstrate a proarrhythmic effect would be the increase in frequency that you demonstrated. If somebody had 50-100 VPC's and you increased it four to five fold, well in the baseline, we see a lot of patients with in excess of 300 PVC's already so I could see he had already approached the upper limit of defining your increment during follow-up especially since we don't know independent of drug therapies, what the time course of that is. In other words, if you got serial Holter's over 6 months or a year without altering treatment whatsoever, would the 300 VPC's go up to 600. Any unexplained sudden death in this population would qualify as a proarrhythmic effect. I am not sure we can define that for a lot of the reasons that everyone has already discussed. Milt has highlighted the key ones in his comments and the absence of other potential causes is along this same line. In other words, if you could demonstrate hypokalemia to the tune of 2.4 maybe you could ascribe it to that, but if somebody has a potassium of 4, that doesn't mean they don't have total body potassium depletion or some transmembrane flux that is inappropriate. How do we deal with these especially in terms of new drugs?
Dr. Morganroth: Patients who have at baseline very high frequencies of PVC's, like you said, 300-500 will be less variable as you follow them over time than those who have much lower frequencies and the criteria we had in that slide suggested a

three-fold increase at that level would probably distinguish a change from spontaneous variability from those patients who had an increase due to the intervention. There are caveats in that: 1) the heart failure population has never been studied for spontaneous variability that I am aware of and the guidelines I just gave are based on the chronic VPC patient who presents usually with an ischemic cardiomyopathy (representing about 70% of the group), or the idiopathic cardiomyopathy or valve disease patients with chronic PVC's and non-sustained VT which makes up the rest. If you will buy that that kind of patient is similar to the kind of patients you deal with, then a three-fold increase going to 900 would be proarrhythmia, going to 600 would not. As I have just said, there is very little data to know that with any degree of certainty in the "indexed heart failure population". Relative to the issue about what do you do with sudden cardiac death. I mean I don't know how to distinguish proarrhythmia from inefficacy. Some of them are going to be proarrhythmic. You have to count them somehow. You could put them in an unknown category but that doesn't help anybody to tell whether there is a problem with the drug. If the event occurs early after starting a drug, I would count it in the proarrhythmia column; if it occurs late, I throw it into the inefficacy column. You could put all of them into the proarrhythmia column or all of them into inefficacy as long as when you compare one drug to another to decide that drug A is bad for the patient vs drug B. There is no absolute basis for lumping it with one group or the other. The same thing about the potassium issue. Obviously if someone's potassium is suddenly 2.4, well why describe a new event solely to the drug. If the K is 4 and it goes down to 3.8, that may be the explanation, or maybe a new clinical factor is responsible but if one is not clearly seen I'd call it proarrhythmia. What do you do with an inotrope that looks good from all the efficacy measures and you are now looking at the safety issue and you find that the drug specifically increases the prevalence of "other proarrhythmia type", that is an increase in PVC frequency? We don't know what that means, but there is no difference in mortality and there is no difference in the serious form, is that enough of a change to be nervous about the drug's safety?

Dr. Temple: Somewhat nervous. You gave an unqualified statement. How well do I know that there is no increase in mortality here. What kind of study do I have in my hand that says there isn't any.

Dr. Morganroth: Let's say the company had done a couple of studies looking at efficacy in which they had some kind of placebo controlled group. Say 150 to 200 a group and there was no difference in mortality. In other words, the usual data base upon which you would approve an inotrope for efficacy and there is no difference in mortality on placebo versus the drug, but there was a two fold increase in "other type of proarrhythmia" but no difference in terms of serious proarrhythmias or deaths. What do you do with it?

Dr. Temple: I think you would agonize a lot naturally. It would take a long time to reach a decision. Do the usual things. In the end I think you have little more reason to think that is bad than you have reason to think that a reduction of that size in most populations is of any value which we don't pending the results of

the CATS study. I think if you had a reasonable assurance that there was no increase in mortality in a study in which there was some mortality so you know it was a reasonable test situation and so on, I would say you would label the drug that way and go on with it. I am confident that its use would be minimal compared to a drug that didn't have that property however. It would probably be reserved for, I just think people would treat it that way, whatever we said in labeling. There is a prejudice against increase in VPB rates just as there is a prejudice in favor of producing neither of which is necessarily based on any data. I don't see why that property would bar a drug if you would explore the possible risks.

Dr.Lipicky: I certainly agree with that, but I just wonder if the idea that digitalis is proarrhythmic has disappeared. Is it no longer proarrhythmic?

Participant in Audience: In toxic doses.

Dr. Lipicky: How do you know what a toxic dose is? I guess all I was saying is certainly one of the major leading agents that is now in use is clearly a proarrhythmic drug. There is reasonable information that it is related to its dose and if indeed someone had data on a new drug that made it look like it was proarrhythmic I would think one would want to see if possible whether or not that proarrhythmic effect was dose related but basically with what you said.

Dr. Temple: Would you find a drug to be approvable if it clearly made people feel better, but clearly enhanced mortality?

Dr. Lipicky: Those are like "when did you stop beating your wife" questions. You have to know a lot more than just those two facts. Those two facts are not enough to know in order to answer the question would you approve the drug or not.

Dr. Morganroth: What would be a key other fact? Or would you like to answer that after the coffee break?

Dr. Lipicky: After.

Dr. Temple: Can this fool rush in where Ray feared to tread. I agree that the question isn't defined enough, but we have certainly said that what we want now with say inotropes, we were a little worried that survival may not necessarily be enhanced or may be in fact impaired, is that it is at least theoretically possible to have some adverse effect on survival. Not an enormous one, you have to be reasonable about this, with a very impressive improvement in quality of life and still have an improvable agent. That is theoretically possible. As Ray said, you have to know some details before you can really give an answer, but I think we have contemplated the possibility and said that it is not out of the question. Obviously, labeling would have to be extremely informative. I mean I think we can say that. We would take it to an advisory committee and obviously it is a matter of important judgment.

III. FDA ENDPOINT ISSUES

10

ARE PLACEBO-CONTROLLED TRIALS NECESSARY IN THE EVALUATION OF NEW THERAPEUTIC AGENTS IN SEVERE CHRONIC HEART FAILURE?

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Evaluation of the efficacy of cardiovascular drugs is complicated by the fact that patients may show beneficial responses during the course of therapy in the absence of effective treatment (1). Patients with coronary artery disease may experience a reduction in the frequency of anginal attacks while on placebo (2,3); patients with systemic hypertension may show small but sustained decreases in diastolic blood pressure while taking no active drug (4); and patients with ventricular tachyarrhythmias may show spontaneous variation in the frequency and complexity of ectopic activity that may mimic a beneficial drug response even if no treatment has been administered (5,6). Such spontaneous therapeutic effects may result from the natural variability of the disease process or from bias introduced by the design of clinical trials. Consequently, in order to distinguish true drug-related effects from those secondary to such spontaneous events, clinical investigators have evaluated the efficacy and safety of new therapeutic agents in the context of placebo-controlled trials. Any improvement noted in the placebo-treated group was termed "the placebo effect"; any effect that could be discerned in the treatment group that was significantly greater than that seen in the placebo-treated cohort could reasonably be attributed to the study drug.

However, early investigations of drugs for the treatment of severe chronic congestive heart failure assumed that, given the advanced severity of the disease process, the placebo effect was probably negligible, and hence, any benefits following institution of treatment could be reasonably attributed to the new therapeutic intervention. If this were indeed the case, then placebo-controlled trials would be unnecessary to prove the efficacy of drug therapy in patients with congestive heart failure. Such a conclusion would make the evaluation of new drugs for the treatment of heart failure infinitely

easier, since placebo-controlled trials are extremely difficult to carry out in this highly symptomatic patient population.

This manuscript will discuss the evidence for (and against) a notable "placebo effect" in patients with congestive heart failure, utilizing data collected from existing placebo-controlled studies and focussing on the four major approaches used in the evaluation of clinical efficacy: (1) symptoms and signs; (2) noninvasive measures of left ventricular function; (3) invasive hemodynamic testing; and (4) objective tests of exercise capacity. If any of these measures remain unaltered in the absence of effective treatment and thus are uninfluenced by placebo therapy, then placebo-controlled trials utilizing such measures would become unnecessary.

Symptoms and Signs of Congestive Heart Failure

The most direct approach to the evaluation of the patient with congestive heart failure is to inquire about symptoms of dyspnea and fatigue at rest and during the course of daily physical activity. This clinical assessment also includes an evaluation of the degree of fluid retention by physical examination or chest radiography. Such an approach is not quantifiable and is subject to considerable interobserver variability, but it is simple and can be directly translated to the practice of cardiology. Since many (if not most) patients with heart failure are considered by their referring physicians to be "refractory" to conventional therapy, any symptomatic improvement seen after entry into a study would at first appear to be logically attributable to the new agent being tested and not to a change in concomitant therapy, since "optimal" concomitant therapy (with digitalis, diuretics and vasodilators) had previously not been effective.

Nevertheless, 20% to 30% of patients who enter heart failure trials improve significantly with placebo therapy (7,8). In part, this may be related to the marked attention that is received by a patient entering a clinical study, which provides enormous emotional support and reinforces compliance with recommendations concerning treatment, which may have been previously made but were ignored. In addition, the effects of many therapeutic interventions (particularly converting-enzyme inhibition) may require prolonged periods of time to achieve optimal benefits (7,9); such therapy may have been started immediately prior to the referral of the patient for study but may not have been given sufficient time for the achievement of full

therapeutic efficacy before the initiation of a new treatment. Such delayed responses to "ineffective treatment" probably contribute importantly to the "placebo effect" reported in previous studies (6).

Noninvasive Measures of Left Ventricular Function

One can evaluate the efficacy of drug treatment in patients with congestive heart failure by observing changes in left ventricular function during the course of therapy, usually by echocardiography or radionuclide ventriculography. Such techniques are objective and quantifiable; furthermore, the left ventricular ejection fraction measured by either technique has been shown to improve significantly during effective treatment in controlled trials and does not change significantly during placebo therapy (7,11,12). Hence, it would appear that such noninvasive measures of cardiac function would provide an ideal measure of drug efficacy.

Unfortunately, such noninvasive measures of left ventricular function do not accurately reflect the clinical status of patients with congestive heart failure, in part because such noninvasive approaches fail to measure changes in regurgitant volume or changes in diastolic function, both of which may contribute importantly to the clinical status of these patients (13,14). The left ventricular ejection fraction as assessed by radionuclide ventriculography does not correlate with the functional state of these patients, and changes in the left ventricular ejection fraction have not been shown to correlate closely with changes in clinical symptoms or exercise capacity (15-17). In fact, left ventricular performance may improve in patients with heart failure who have deteriorated clinically during investigational drug treatment (18). When this occurs in the absence of a placebo-treated cohort, the observed worsening of symptoms may be ignored because it is incorrectly attributed to the natural history of the disease, and in so doing, the increase in left ventricular function may be incorrectly taken as definitive evidence for drug efficacy.

Invasive Hemodynamic Testing

Although associated with the risk (albeit small) of right heart catheterization, invasive hemodynamic measurements are objective and quantifiable, and thus, have provided the most commonly used approach to the measurement of drug efficacy in most trials of drug therapy for heart

failure. Two invasive procedures are generally required to gauge the response to treatment, however, since short-term changes that follow the administration of single doses of a new drug fail to predict the long-term benefits (or lack thereof) of a new intervention (9,19,20). Hence, for hemodynamic measurements to have meaning, right heart catheterization must be performed twice during the course of therapy, the first during drug initiation and the second after 1 to 3 months of treatment. When such short- and long-term measurements have shown marked and sustained hemodynamic improvement in controlled studies, they have provided important evidence for drug efficacy, especially when similar changes were not seen during treatment with placebo (12,21,22).

Unfortunately, hemodynamic changes mimicking a beneficial drug response can occur in the absence of effective treatment under three specific conditions. First, intravascular instrumentation appears to elicit notable systemic vasoconstriction, the dissipation of which (over 12 to 24 hours) can closely mimic a beneficial drug response (1). If pre-drug measurements are performed during this immediate post-catheterization period, all subsequent measurements can be interpreted as showing a beneficial drug response when compared to the artifactually vasoconstricted state at the start of treatment; similar degrees of systemic vasoconstriction may not be elicited during a second invasive procedure. Second, vasodilator responses may follow the administration of meals; such immediate postprandial events likely explain many of the hemodynamic changes that have been reported to occur following the administration of placebo (23). Third, if data are analyzed looking for a "peak drug effect" and comparing this value with the pretreatment hemodynamic state, most drugs can be interpreted as being efficacious, since inherent in the concept of a "peak drug effect" is that a true drug effect has indeed occurred (24). By looking at spontaneous hemodynamic fluctuations and examining the data for maximal changes in each variable regarding of the time of occurrence, it is possible to show that all interventions are capable of producing statistically significant changes. To avoid the biases inherent in the three situations outlined above, investigators should (1) wait 12-24 hours after right heart catheterization before performing pretreatment hemodynamic measurements prior to drug administration; (2) keep patients in a fasting state (except for liquids) throughout the period of invasive measurements; and (3) analyze data

utilizing predefined time points after drug administration, at which all hemodynamic variables are determined and compared with pretreatment values.

Investigators must also be careful about defining the hemodynamic goals of long-term drug therapy in chronic heart failure before the initiation of the clinical study. Although striking, drug-induced increases in cardiac output and decreases in systemic vascular resistance are not generally translated into clinical benefits (8,18), but most drugs that have been shown to be beneficial in placebo-controlled studies have produced marked and sustained decreases in right and left ventricular filling pressures during long-term treatment (12,21,22). The finding that a new pharmacologic intervention can produce decreases in right and left ventricular filling pressures for 1 to 3 months is not sufficient to merit definitive conclusions concerning drug efficacy, but it provides important encouragement in pursuing further studies to confirm the drug's beneficial clinical effects.

Objective Exercise Testing

Exercise testing has long been used in the assessment of drug efficacy in patients with stable angina pectoris, but it has been only recently used in the evaluation of patients with congestive heart failure. The measurement of exercise duration is objective and quantifiable, and has been shown to improve significantly during effective treatment in controlled clinical trials (7,12,21,22).

Unfortunately, the duration of exercise in patients with congestive heart failure is highly dependent in the motivation of both the patient and the physician. 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. Submaximal tests in patients with heart failure can in part be detected by measuring the respiratory gas exchange ratio; the failure to achieve a ratio greater than 1.0 indicates that exercise has not ceased because of factors related to circulatory function. If respiratory gas exchange is not measured, exercise duration may improve following short- or long-term placebo therapy and may be large enough to mimic a therapeutic drug response in the absence of effective treatment (8,10,25).

Some investigators have suggested the measurement of maximum oxygen uptake as an objective measure of exercise capacity in heart failure, which is independent of patient motivation and thus is uninfluenced by placebo treatment (26). The accuracy of this measurement, however, requires that a maximal effort has been made, and this can only be convincingly shown if a plateau in oxygen uptake is achieved by the patient during the final 30 to 60 seconds of exercise. Unfortunately, such a plateau rarely, if ever, can be demonstrated in patients with congestive heart failure (27). Hence, even the measurement of peak oxygen uptake is subject to patient motivation; increases up to 25% in this variable can occur with repeated exercise in the absence of effective therapy (28). As a result, peak oxygen uptake may increase significantly during treatment with placebo (29).

Conclusions

A number of approaches have been proposed to evaluate drug efficacy in patients with congestive heart failure, and most have been shown to improve during the course of effective drug treatment. However, all of these parameters may also improve during placebo therapy or may fail to parallel important changes in clinical status. Such unexpected responses may result in part because of inexperience of the clinical investigator, who may not have put into place the appropriate quality controls to ensure reproducible measurements of hemodynamic variables or exercise capacity. On the other hand, even the most experienced investigator will occasionally attribute the benefits seen during a trial to the study drug, even when no effective therapy has been administered. Since no variable that accurately reflects the clinical status of patients with heart failure is free from the influence of the "placebo effect" (30), placebo-controlled trials are mandatory in the evaluation of new therapeutic agents in the treatment of congestive heart failure.

REFERENCES

1. Packer M, Medina N, Yushak M. Circulation 1985; 71: 761-766.
2. Evans W, Hoyle C. Q J Med 1933; 2: 311-338.
3. Cole SL, Kaye H, Griffith GC. Circulation 1957; 15: 405-413.
4. Moutsos SE, Sapira JD, Scheib ET, Shapiro AP. Clin Pharmacol Ther 1967; 8: 676-683.
5. Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB. Circulation 1978; 58: 408-415.

6. Winkle RA. Circulation 1978; 57: 1116-1121.
7. Captopril Multicenter Research Group. J Am Coll Cardiol 1983; 2: 755-763.
8. Franciosa JA, Weber KT, Levine TB, et al. Am Heart J 1982; 104: 587-594.
9. Packer M, Medina N, Yushak M, Meller J. Circulation 1983; 68: 803-12.
10. Massie B, Bourassa M, DiBianco R, et al. Circulation 1985; 71: 963-971.
11. Colucci WS, Wynne J, Holman BL, Braunwald E. Am J Cardiol 1980; 45: 337-344.
12. Leier CV, Huss PM, Magorien RD, Unverferth DV. Circulation 1983; 67: 817-822.
13. Urquhart J, Packer M, Patterson R, Horowitz SF, Micelli K, Gorlin R. Am J Cardiol 1980; 47: 498 (abstr).
14. Brodie BR, Grossman W, Mann T, McLaurin LP. J Clin Invest 1977; 59: 59-68.
15. Firth BG, Dehmer GJ, Markham RV, Willerson JT, Hillis LD. Am J Cardiol 1982; 50: 954-959.
16. Engler R, Ray R, Higgins CB, et al. Am J Cardiol 1982; 49: 1832-1837.
17. Franciosa JA, Park M, Levine TB. Am J Cardiol 1981; 47: 33-39.
18. Franciosa JA, Jordan RA, Wilen MM, Leddy CL. Circulation 1984; 70: 63-68.
19. Franciosa JA, Dunkman WB, Leddy CL. J Am Coll Cardiol 1984; 3: 1521-1530.
20. Massie BM, Kramer BL, Topic N. Circulation 1984; 69: 1135-1141.
21. Kramer BL, Massie BM, Topic N. Circulation 1983; 67: 807-816.
22. Sharpe DN, Murphy J, Coxon R, Hannan SF. Circulation 1984; 70: 271-278.
23. Cornyn JW, Massie BM, Unverferth DV, Leier CV. Am J Cardiol 1986; 57: 238-241.
24. McKay CR, Nana M, Kawanishi DT, et al. Circulation 1985; 72: 865-872.
25. Franciosa JA, and the Captopril-Digitalis Research Group. J Am Coll Cardiol 1985; 5: 513 (abstr).
26. Weber KT, Kinasewitz GT, Janicki JS, Fishman AP. Circulation 1982; 65: 1213-1223.
27. Wilson JR, Fink LI, Ferraro N, Dunkman WB, Jones RA. Am J Cardiol 1986; 58: 601-606.
28. Le Jemtel TH, Mancini D, Gumbardo D, Chadwick B. Heart Failure 1985; 1: 112-124.
29. Leier CV, Binkley PF, Randolph PH, Unverferth DV. J Am Coll Cardiol (in press)
30. Packer M. J Am Coll Cardiol (in press)

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WHAT THE FDA REQUIRES FOR ENDPOINT MEASURES IN CONGESTIVE HEART FAILURE STUDIES

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I cannot significantly add or detract from the kinds of things that people have talked about measuring so far in this meeting, nor alter the way in which people think about what those measurements mean. Although there are no specific requirements that can be delineated, there is substantially good advice I think that can be given.

From my vantage point the most important factor is that the entire data base makes sense. If one found an isolated measurement that is improved by placebo therapy, one would not reasonably expect approval of placebo. Although one might say that "mechanism" is unimportant to the approval process, unless there is some framework of reference to hang the apparent clinical benefit on, people are quite reluctant to accept an empirical finding as fact. An isolated finding, needs to be established with an enormous amount of certainty or one needs to bring some other framework of reference to bear on explaining why an isolated finding was a clinical benefit and therefore approvable. I think the way in which any of the particular endpoints are interpreted depends on the kind of model that one believes in. If one's model asserts that something for the treatment of congestive heart failure must improve the function of the heart, then if one looks at the relationship between filling pressures and output, one expects a certain way for those variables to change, otherwise, one can't conclude that heart function was helped. However, if one looks at the variables that are being measured from some other model, one may well come to a different interpretation of the way in which those variables should correlate. It is difficult to know what kind of model one carries around in one's head. It is really necessary, I think, when one asks the question: does so-and-so make this approvable? to clarify how one is thinking about congestive heart failure and what model one is invoking when making the judgment as to whether something makes sense or not.

The last generalization is that the things that one expects to have to measure, and the way in which one expects those measurements to behave over time, may vary and depends upon what is learned from trials in progress. Consequently, if one had started out in congestive heart failure a few years ago without placebo controls, one would today encounter a very adverse judgement even though when the program began it may have made all the sense in the world.

Requirements change continuously and I don't see how I can guarantee that anything I say today would be applicable six months from now.

What is good advice? I guess good advice starts at the patient level. When patients are enrolled into the trial, it would be quite reasonable to make measurements that did at least two things. First, establish and document that these patients had congestive heart failure. Secondly, look at the cardiac function in these individuals and attempt to make some kind of distinction with respect to whether this was mainly diastolic malfunction, systolic malfunction, or a mixed malfunction. The nature of the abnormality that exists in the patients may become critical at the time that analysis occur. At least one should prove that patients in the trial had heart disease and that their hearts were not functioning normally at the time that they were enrolled in the trial.

I can't conceive of a trial in congestive heart failure that is of a chronic nature that does not measure exercise tolerance. I subscribe to the idea that exercise intolerance is the way in which the syndrome is identified. I would assert, although this is debatable, that if one cannot find an increase in exercise tolerance for a treatment regimen that is given for the treatment of congestive heart failure, then one has some explaining to do, or that some other finding in the trial needs to be quite spectacular to offset not having found a change in exercise tolerance. What type of exercise tolerance measurement to use is unknown, but I would do more than one kind. I'd do maximal exercise, measure VO_2, etc and treat them as separate variables, and I'd try to get an anaerobic threshold.

Although the symptoms and signs of congestive heart failure are indeed difficult to quantitate and are usually "pretty messy." At least the New York Heart Association has been shown to be useful from the vantage point of making a differentiation between an active drug and placebo, so that would be a minimum criterion. A system might be devised that quantitated symptoms or signs in some more adequate fashion. There is nothing wrong with devising some new system since one ought to have a control group and would be able to compare control to drug.

There should be a serious attempt to track events. The presence or absence of arrhythmias certainly should be something that is measured. Whether it be by Holter or by invasive techniques is debatable, but certainly there should be measures of whether or not arrhythmias are present or not and the arrhythmias should be characterized. More than that, the features of the patients at the times that arrhythmias might or might not have been detected, need to be carefully documented; whether the potassium was up or down on the day of the Holter that saw the VPC's, should be something that one provides for in the data collection process, and if one doesn't make that a special attempt to provide for that, information is generally lost. Similarly, one should also consider the hormonal status.

Quality of life is something that ought to be measured in some way, because you don't know who it is that will be looking for that data and whether or not there will be adverse effects that need to be overcome. When evaluating approvability the risk-benefit assessment is being weighed and it seems foolish to not include

measurements of all potential benefits.

Lastly, hemodynamics need to be documented. If one doesn't have any measurements that say that hemodynamic status is changed by drug and is maintained in some changed status over at least the course of the trial, how can one evaluate that set of data when it comes to evaluation time? From a hemodynamic point of view, I think we have generally had the policy that for short-term treatment of congestive heart failure, hemodynamic changes are appropriate and are acceptable as primary evidence of efficacy even in the absence of any documentation that those hemodynamic changes altered the patient's symptomatology, quality of life, or exercise tolerance, or anything else. Once beyond a few hours or a day or so, hemodynamic changes alone are totally insufficient to address the question of longer term use. If an agent available for parenteral and oral use had acute hemodynamic events that were appropriate, a judgment really wouldn't be able to be made on approvability until the chronic, oral data were available to review.

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DESIGN OF TRIALS TO ASSESS SAFETY AND EFFECTIVENESS IN Rx OF CHF

ROBERT TEMPLE, M.D.

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It is a propitious time to consider drugs for the treatment of congestive heart failure (CHF). There is at present a great deal of academic and commercial interest in such agents, perhaps reflecting an early success, captopril, and a partial success, amrinone IV, after a good deal of ambiguity and failure with prazosin and the beta agonists. Yet there is still a great deal to be learned. We do not yet know how much it is possible to achieve or what hemodynamic or exercise responses to drugs correspond best to clinically meaningful improvement.

The features that make the meeting propitious also make my task, and Dr. Lipicky's very difficult. We have been, in effect, asked to develop before your eyes a clinical guideline for drugs intended to treat CHF. Anyone who has been part of guideline writing in some comparatively clear cut situations, e.g. antianginal drugs and antiarrhythmics, knows that developing a guideline is the task of a year or two - not a day or week. So lower your expectations. I consider

antianginal and antiarrhythmic drugs "easy" because FDA has reviewed numerous drugs with these activities over more than a decade. We therefore have a great deal of experience in considering NDAs and advising sponsors at end of phase II conferences, and we have some old guidelines to start with. Here, with CHF, we start with almost nothing: no real track record, few completed reviews, no sure knowledge that what we think is reasonable will prove to be so, and a state of constant revision of ideas of what measurements mean - including doubts, new to me, even about maximal exercise tolerance. We also seem to see some surprising results, e.g., drugs that seem to work when added to diuretics and digoxin but may not when used alone; well designed studies that give inconsistent results; and drugs that work for a while, then stop. We cannot tell yet whether such surprises merely reflect the inherent variability of clinical situations or reflect real findings; we simply aren't yet smart enough in these areas to anticipate outcomes. All this means that it will be possible for me to offer some general principles, but that everyone should stay alert to change.

In considering the design of trials to assess safety and effectiveness of a drug class, it is usually useful to review our past actions: In CHF we do not yet have many real-life examples to work from and some of those we have are untypical. There are three (3) treatments that have been approved for chronic treatment of CHF:

diuretics, digoxin, and captopril.

1. Diuretics probably are not a good example, as they are nominally indicated not for CHF but for edema or fluid retention. The only effectiveness measures required have been weight reduction or elimination of visible edema. We have never asked for evidence of improved NYHA classification or improved exercise tolerance. Perhaps if we had, as Dr. Jessup told us earlier, diuretics would have done very well, but the requests were not made. Only one loop diuretic, the kind of diuretic most clearly directed at heart failure, has been approved in the modern era; two thiazide-like agents have been approved in the last 15 years, but treatment of edema was a relatively minor secondary claim; hypertension got most of the attention.

2. Data supporting effectiveness of digoxin has been looked at recently, but with the deference due to a venerable relative. There is good evidence that well chosen patients (i.e., those with a history of pulmonary edema) on digoxin develop worsened CHF, assessed clinically, not by exercise testing, when digoxin stopped. Our digoxin review was of the DESI type; it reassured us that the molecule was effective, but we did ask for the systematic evaluation a new agent

would be expected to have.

3. The approval of captopril was recent and reflects a more modern standard; we have evidence of acute (presumably) favorable hemodynamic effects, including resting cardiac output, improved ejection fraction, and decreased filling pressure. The critical clinical study was carried out for 12 weeks in NYHA III and IV patients already on optimal digoxin and diuretic therapy; it was a placebo-controlled randomized trial that assessed treadmill exercise tolerance, change in NYHA classification and clinical symptoms, as well as hemodynamic measures. By all 3 clinical measures, as well as hemodynamics, captopril was superior to placebo. We did not ask specifically about mortality as we had no particular concern that a vasodilator would be arrhythomogenic or have other adverse consequences, and we were not prepared to argue that proof of improved survival was a necessary condition of approval, so long as clear clinical benefit was seen.

The study did, in fact, show a small favorable, but non-significant, trend for captopril on mortality. Apart from providing evidence of effectiveness, this trial also showed that the clinical course of a fairly sick population over

a three (3) month period is not relentlessly downhill; the placebo group did not deteriorate on average and some patients improved considerably. Ultimately, of course, the decline shown by Ed Sonnenblick surely would have been seen, but it was not seen in three months.

With this brief background, let me turn to consideration of the design of trials in CHF. The compounds I have had in mind while developing these thoughts are those with inotropic or vasodilator properties, but the same principles should apply to an agent based on a completely different theory or mechanism. (Any good guideline should give guidance for effectiveness studies that is more or less mechanism independent). I share the bias expressed by others that when how to proceed is not very clear, it is prudent to utilize several kinds of study design, to take extra pains to define patients fully, and to measure all reasonable parameters. It is too early for parsimony.

I will first consider the features of a single trial, then turn to the mix of data from all trials that should be collected.

1. General design features/end points.

   It can be taken as a given that approval of drugs for the treatment of CHF will be based on reasonable measures of clinical improvement, not

on hemodynamic or cardiac functional changes alone. We are of course interested in collecting data on how various measurements of cardiac function correlate with clinical effects and at some future time it is conceivable that such measurements would achieve the status of definitive end points. But not yet.

As many of the important clinical measurements have subjective elements, or could be influenced by investigator bias, critical studies should use the usual measures to reduce bias, including a placebo or other control, randomization and blinding. As in all trials with multiple measurements, prior specifications in the protocol of critical outcome measures, inclusion criteria and analytic plans, is vital.

2. Dose selection

It is very difficult to provide good general guidance on dose-selection except to say that it is crucial, before moving to trials, to have excellent data on the dose-response of measurable pharmacologic effects and adverse effects. This is especially critical in trials where hemodynamic measurements will not be used to titrate patients.

Given the difficulty there has been in showing clinical effects of drugs in CHF, it does not

seem a bad idea to study more than one dose or to titrate in some way to the highest tolerated dose, at least in early trials, to seek a maximal response. Once having shown a clear effect, rigorous dose-response data would need to be obtained. What would seem ideal, if it could be done, would be to seek correlation of clinical effects with one or more pharmacodynamic responses. For example, groups could be titrated to several defined levels of increase in resting or cardiac output, change in ejection fraction, or fall in filling pressure and clinical results compared in the groups. Aside from producing a very good, persuasive kind of evidence, the study might give unusually good guidance in how to use the drug and how to identify responders.

3. Dose interval

There is not a lot of guidance as to how long effects of agents with various properties can be expected to last. Diuretics, of course, have prolonged effects, presumably because sodium, once lost, takes time to reaccumulate. In early studies treatment will presumably be given relatively often, based on half-life. If these studies are successful, less frequent dosing could be tried. Again, good data on the duration of hemodynamic effects may help anticipate the duration of clinical benefit.

4. Patient population

Patients obviously need to have the characteristics whose improvement will be used as effectiveness end-points, such as high NYHA classification, decreased exercise tolerance, particular CHF symptoms, decreased cardiac output, decreased ejection fraction, elevated filling pressure or, in a mortality trial, features indicating high risk.

Aside from the need to have testable end-points, it seems very prudent to characterize patients extremely well by etiology of CHF, presence or absence of exercise or vasospastic angina, arrhythmia status, including history and Holter results, and any other feature that could affect prognosis or response. This will allow for subset analyses, should overall results be disappointing, and the possibility of explaining good or poor results. Any subgroup successes would, of course, need to be confirmed in prospective studies.

5. Monitoring

The pertinent end-points have already been considered; these will of course, be measured throughout the study. I do not want some of my remarks earlier in the day to be misunderstood; I said that I think any reasonable, clinically

meaningful response could be a basis for approval of a claim, even if a plausible hemodynamic mechanism does not exist and even if not all clinical measurements are improved. I did not suggest that a full range of measurements should not be made. It is critical to carry out measurements of all reasonable clinical and hemodynamic parameters, if for no other reason than to be sure there are no adverse consequences of treatment. You need to know as much as possible about what a drug does to assess its risks and anticipate potential problems. I therefore want to emphasize the need, at least at this stage of our understanding, to measure as much as possible. When the effectiveness and hemodynamic responses to the drug are well established, longer-term and safety studies can be more selective in what is recorded.

Certainly, at a minimum, one wants some measure of hemodynamic response, preferably in both resting and exercise states, over the course of the study, as well as effects on exercise tolerance, symptoms and NYHA classification. It seems certain that more sensitive quality of life or life function scales can be developed and, once they have gained credibility and acceptance, they should be used.

6. Design

Parallel designs are easier to interpret and less subject to "accidents" due to dropouts, unstable baselines, etc. Crossover designs thus seem to represent some risk, although I would not say they could not work if care were given to re-establishing baseline between treatments.

There is a minor role for withdrawal periods at the end of long-term studies. They would be useful if added to an otherwise well-designed study, but not very helpful, I think, added to an open trial.

Let me now turn to the kind of overall database to be expected:

1. Clinical Pharmacology

It is particularly important to enter controlled trials with a well characterized drug. I know clinical pharmacology studies are not thought to need controls in many cases, but there is need for caution here. You do not want better compliance with background therapy or an unperceived change in activity level to be confused with drug effect. The Oates-Woosley design used in arrhythmia studies should be considered for CHF: titrate patients in open fashion to a maximally tolerated, or fully effective dose, withdraw therapy, and confirm the

open result in a randomized trial of placebo control versus the dose to which patients had been titrated.

In any event, it is critical to gain early understanding of the effects of the drug on resting and exercise hemodynamic state and the dose-relationship of these, and other effects. While study can be started in patients with mild to moderate abnormalities, it is important also to move to more abnormal people because history tells us they may respond to drugs very differently.

It seems wise also to explore pharmacologic effects in the presence of likely concomitant therapy, including digoxin, diuretics, ACE inhibitors, and perhaps other vasodilators to see whether the effect is the same. Is there, e.g., a suggestion that the dose-response has been shifted due to the other drug.

It is worth observing that these early attempts to explore a drug's properties should be carried out in a spirit of openness and flexibility and with a reasonable number of highly qualified investigators. It is a mistake, I believe, to rely on a single investigator and to hide away from the world. Years ago the drug industry lobbied hard for FDA flexibility on early

studies: "don't lock us in to rigid protocols," they said: "early on is when good investigators should be able to follow their instincts, pursue leads, etc." We were convinced by this and our proposed IND regulations reflect it. I'm not sure sponsors are really convinced , because what I hear is that companies try hard to limit "lock in" these investigators to specified designs, leaving little discretion. I also know that investigators whose findings are not as favorable as others, or who express concerns about potential problems, are sometimes ostracized, not given further access to the drug. This is, I think, a serious error, with risks for the public and the sponsor. If, among carefully chosen investigators, different or adverse results are obtained, it is critical to find out why - it is senseless to presume the investigator with adverse findings is prejudiced or wrong. I cannot prove this, but I believe clues to important problems often exist early, but are missed, only to be rediscovered later. Do <u>not</u> play the winner and think you're home free; the truth must out and the sooner it is found, the better.

2. Controlled Trials

The database needs to include placebo controlled trials showing effectiveness or, alternatively,

it could include some other design that allows a demonstration of a difference between treatments. A parallel dose-response study, comparing several fixed doses, is an excellent design, as is showing superiority to an active control group that is at least known not to be harmful.

If I were doing these studies, I would always use an active control as well as placebo, if there is a reasonable active control. You want to know, if a study doesn't work out well, whether a problem is the study (e.g., population, design, investigators) or the drug. The active control should tell you. This design is not necessarily perfect. An ACE-inhibitor control for an isotope, for example, could raise interpretation problems; it is at least possible that a particular population could respond to one but not the other.

Very sick patients need to be studied because they will be given the drug once it is marketed. Even severely ill patients can be included in controlled studies if there is provision for early escape in the event of deterioration. It is of very great value to have a control group if very sick patients are entered, because it permits interpretation of the adverse events that are certain to occur in such populations.

One definitely wants to know how a new agent behaves in the presence of other agents used to treat the same disease; eventually, therefore, there should be controlled trials in patients:

a. On no therapy.
b. On diuretics
c. On digoxin (or perhaps digoxin and diuretic together).
d. On captopril (except if the new agent is another ACE inhibitor).
e. On an inotrope (if one is approved).

Not all of this information needs to be obtained prior to approval. Captopril, e.g., was approved based on studies using a digoxin/diuretic baseline; there was no study of the drug alone. In addition to short and medium-term placebo controlled data, longer studies are needed. Realistically, one cannot usually expect 6 months of placebo in NYHA III or IV patients so that active controls may be needed. It is critical, however, to be sure that the drugs in the long-term trial were effective short-term. My recommendation would be that if long-term placebo is not possible, the study should start as a three-way trial and drop the placebo after a time, continuing with test drug and active control. An end-study withdrawal phase is a good

idea after a long-term study to show persisting pharmacologic effect.

> In controlled trials, special attention should be paid to possible worsening of concomitant conditions. Until it is very clear that the drug is not proarrhythmic periodic Holter monitoring at least should be carried out in a fraction of patients. Note that there could be differences in proarrhythmogenicity between more and less severely ill patients. Attention to angina status is important also. Treadmill testing to a pain end-point will not be possible here in patients with severe CHF, but certainly a suitable questionnaire could be utilized.

We have not felt that it was appropriate to require that drugs for treating CHF must improve survival, as there can be meaningful clinical benefit without this, but we want reasonable assurance that survival in high risk patients is not impaired. The controlled trials thus need to be of sufficient size to detect a substantial increase in mortality. Given the high mortality in NYHA III and IV patients, this does not demand a very large study in this group.

I think what Ray and I have said can be easily summarized: Find a drug with a plausible mechanism. Do good, very thorough clinical pharmacology. Then examine the drug in well controlled studies of adequate size in patients with a full range of CHF severity measuring effects on all of the relatively obvious appropriate end-points. So far, at least, it has not proved to be easy to do this. The reason may have been, at least in part, especially for inotropic agents, the understandable excitement over the new possibilities has gotten in the way of patient, orderly development. This seems to be changing.

DISCUSSION - 3

Dr. Bigger: Dr. Temple, when considering the active and the placebo groups in heart failure studies, what is the impact of the power issue? If you have a group of people who are sick, enrollment may be biased to begin with, the population is very variable and if you split up your patient groups into multiple treatment limbs what happens to the power?

Dr. Temple: You would have to carry out a bigger study than you would have otherwise to include an additional group. The primary measurement of comparison of interest here is the test drug and the placebo and so I don't think power considerations would change there. You would need the same number for that comparison as you would otherwise need. If you were trying to make an important comparative statement about the two active drugs, those two groups would have to be much larger, but I don't think that is the intent here. To me it is get a reasonable point estimate of how they work and then have some explanation if your drug doesn't work. If your drug doesn't beat placebo, you want to know whether the standard did too. It's really there for that purpose. Enough of these studies are not coming out successful that I think a case can be made for taking that precaution. As far as the regulatory agency goes, a study in which the known effective agent doesn't show effectiveness and the new agent doesn't is a nullity we wouldn't tend to raise any doubts about the drug whereas the trial of adequate study that fails to distinguish drug and placebo in the absence of an active control makes you wonder and somewhat counts against it

Dr. Somberg: Two questions. One to Bob Temple. You sort of stated that you didn't think there would be benefit from a withdrawal of placebo in for instance an open study, but there is an event or there is a need at least from a clinician's point of view for at times turning to new drugs in a population that nothing is working on, that fellow who is gasping at the bedside. If you do stabilize the population that serves really no benefit to the sponsor of the compound. In fact there is a great danger if you don't stabilize a lot of people and there is a demise on their drug, would not those people who are stabilized benefit, or would not the sonsor benefit from those people who are stabilized being withdrawn at some point baseline on drug measurement, then you get off drug measurement taking into account what Dr. Packer pointed out as the potential effects on the initial catheterization.

Dr. Temple: I guess my only concern about these is that it is not so easy to interpret them unambiguously. If the idea is to put a patient *in extremis* on therapy and let say you see something that looks like a plausible benefit, if that kind of observation is reliable, then you don't need any control at all. If it is not reliable, then the question becomes, what do you learn if you now remove the drug. Ordinarily, I guess I would say that probably does provide some evidence that the drug was continuing to have an effect if hemodynamic parameters become impaired. What it doesn't tell you as far as primary evidence of effectiveness goes is whether on the whole you have done anything good. This kind of thing came up in discussions of amrinone. You saw improvement in

certain parameters, in open studies, and then the gradual drift down. When you took the drug away, they got worse. Is that evidence of overall benefit? It is hard to say because it doesn't allow you to reach a conclusion about what all that open period meant. Really all I wanted to say was that the usefulness of this as primary evidence of effectiveness I think is more doubtful than in some other cases. It is still of interest to know what happens when you take a drug away. I think that is one of the things you should know about any drug, how to discontinue it, so studying withdrawal and seeing if there is a withdrawal phenomenon, that kind of thing I think is useful. I don't think it is going to be helpful as primary evidence of effectiveness, but maybe that needs more discussion.

Dr. Somberg: The second part of my question was to Dr. Packer and it relates to placebo. I agree with you that in fact your evidence is very compelling for its need, but how does a company that has an investigator or a clinician deal with a problem that there are certain approved drugs that have demonstrated efficacy. So how do you deny patients or what patients would deny these and only give them placebo or is digitalis and diuretic placebo in your mind.

Dr. Packer: I would like to address that question at the same time as the question that Bob Temple raises as to whether one can do placebo controlled trials in patients in extremis. I think that patients who have class 7 heart failure are patients who are extremely difficult for ethical reasons to randomize, but they provide a wonderful substrate for the evaluation of potential benefits and hypotheses be tested in a prospective action in the future, that is, that if you in an uncontrolled study, you could use patients like that to define dose response relationships. You can use patients like that to define uncontrolled hemodynamic and clinical benefits. These are all things that need to be tested further in the patient population that you can study. I think that the other thing that these studies provide is safety data in that kind of severe patient population who may be particularly prone to certain side effects of vasodilator or inotropic therapy. In terms of background drug therapy, it is an extremely difficult question. Almost all of the trials that have been done to date have used a background of digitalis and diuretics and we had evaluated placebo on top of that background. It is not that these patients are on no therapy, they have a steady state, which has been "stabilized" on digitalis and diuretics. The problem with using a steady state stabilized on Captopril is the following and this was particularly marked in the Amrinone multi-center trial. It takes a long time for the effect of Captopril to be manifest and to remain in steady state conditions, i.e. when you see that progressive improvement over time, depending on the point in which you would like to enter that patient into another study, does the patient have to be on the converting enzyme inhibitor for two weeks, a month, two months, three months? It is extremely difficult to know and that kind of beneficial drift can account for some of the placebo effects seen in some studies. We do not have major ethical concerns about randomizing patients or not taking patients and putting them on Captopril because we are still in terms of Captopril discussing symptomatic benefit and if we can find another symptomatic benefit

in a short term trial, i.e. two or three months, I don't have any major ethical concerns our IRB has not had major ethical concerns either. The question of survival with hydralazine and nitrates is very very pertinent. It would be extremely difficult to study hydralazine and nitrates as background drug therapy and then add an end study drug onto that. I think one can get around that if one says that 3 months is not a long time. However, for these patients it is a long time and we are talking potentially 25% of their anticipated life expectancy. Nevertheless we have not had a problem doing that in terms of our local IRB or our feelings about drug therapy.

Dr. Laidlaw: This is a question to Dr. Packer. You partly answered my question because you stated that your placebo is not really placebo but is digitalis and diuretics, yet in our studies, some of the patients have improved when they are on placebo, but some of them have not improved. They have worsened: they have had symptomatic congestive heart failure, they have developed atrial fibrillation and it is one of the problems. They have had to drop out as unanalyzeable data so we end up with not following this group through to completion, comparing then a selected population. What I would like to know is with these people who are early failures, if you go through a placebo lead in period, how would you study these patients so as to incorporate that information in the study design.

Dr. Packer: Are those patients who are sufficiently unstable that they drop out in the three month trial on placebo?

Dr. Laidlaw: Right.

Dr. Packer: No matter how much you attempt to stabilize patients prior to entry into a trial you are going to get drop outs in heart failure. It is the nature of the process and they are unfortunately unpredictable. The care that you take to try to insure clinical stability. Anything you can do to do that is going to reduce your drop out rate. If you have a run in period for 5 days, you are going to have a high drop out rate. If you have a run in period for 1 month, you are going to have a correspondingly low drop out rate. I think in terms of how you analyze those patients in terms of the total data base, there is a potential bias thrown into the system if you are only analyzing completers in any trial.

Dr. Fisher: I think intention to treat analyses would include all randomized patients, which is necessary to do in the situations you are describing. You are driven to rank order sorts of methods so you can add the drop outs and failures and analyze it in several ways, but typically as failures. Dr. Packer mentioned the difficulty of testing something where there is a 30% placebo response and then you have a drug that works in 35% of the time of what you said and I am sure you didn't mean the drug worked in 35% but actually you came out with a favorable result in 35% and I just wanted to point out that in fact if the drug worked in 35% and if that 35% was statistically independent of the 30% placebo response, by the time you put it all together you would have a 54½% response which in fact you could get at, so that in this area if a drug works in 35% you would be doing quite well and could attack it. On the other hand, if your response is favorable in 35% probably the

drug works in about 5% of the people and 30% of that response is then a placebo response and it is hard to get too excited about missing a drug like that.

Dr. Lipicky: A quick comment on trial design where dig and diuretics are in the background and then it is placebo versus drug and that solves the ethical problems. In some ways it does, but our action on trials of that nature is to label the drug then in the setting that the clinical trial data supported it which kind of then makes it second line or third line therapy which is in fact where the agents are now. There is no data that says this is where they deserve to be. That is an artifactual circumstance so that if it is not clear that one shouldn't be doing trials without the dig and diuretic background in which case, what would you say with respect to placebo and you don't have dig and diuretics from the same point of view of whether it is O.K. to use placebo in milder patients and whether you would have IRB problems.

Dr. Packer: I think that any indication has to be taken in the context of what is routine clinical practice. I think that if you can identify a certain patient population in which there is no particular strength of a mandate for digitalis and diuretic therapy, I would have no ethical problems. I am saying not proof of efficacy for digitalis and diuretics but the concept that clinical experience at present time suggests that withholding diuretics in patients i.e. with classs 4 heart failure will be very difficult to approve. I think it has to be taken that IRB's don't look at what is proven necessarily as well as what is the clinical context in that community and it is ethical in terms of that clinical context and I think that the absence of background digitalis and diuretics will be progressively more acceptable i.e. in certain patient populations and for certain kinds of hypotheses.

Dr. Lipicky: Is that a yes, you can do placebo control trial answer?

Dr. Packer: Yes.

Dr. Temple: There is a therapy that at least in mild congestive heart failure appears to improve mortality. That hasn't really been discussed. It seems to me that perhaps after the VHEFT trial is discussed a little more, that is going to become an important factor in all these trials.

IV. THERAPEUTIC STRATEGIES

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HOW DOES CONGESTIVE HEART FAILURE ALTER RESPONSE TO DRUGS?

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INTRODUCTION

The process whereby administration of a drug results in pharmacologic effect depends on two major sets of variables: pharmacokinetic and pharmacodynamic factors. Pharmacokinetics refers to the relationship between dose of a drug and resultant drug concentrations (parent or metabolite; plasma or tissue). Methods to study the impact of variables such as age, disease state, or concomitant drug administration on plasma pharmacokinetics of drugs and metabolites have been fairly well worked out. It is convenient to think of pharmacodynamics as the relationship between drug concentration and effect. Although it is widely recognized that drug effects may vary among patients despite equivalent drug concentrations, methods for quantifying these pharmacodynamic differences are generally unavailable, so quantification of interindividual variability in drug "sensitivity" remains largely descriptive.

PHARMACOKINETIC FACTORS

The Therapeutic Window

Although it is possible to quantify the disposition of most drugs, this mathematical exercise assumes particular importance when it has an impact on drug dosing. For drugs with narrow margins between concentrations associated with efficacy and those associated with toxicity, a detailed evaluation of the factors responsible for interindividual variability in drug concentration (Table I) may clearly allow safer and more effective drug therapy. As described below, pharmacokinetic studies can also indicate, even for drugs with fairly wide margins between concentrations associated with efficacy and those associated

Table I: FACTORS PERTURBING THE RELATIONSHIP BETWEEN DRUG DOSE AND EFFECT

Pharmacokinetic factors:
Absorption
Distribution
Metabolism and Elimination
Disease states
Genetic factors
Other factors (age, smoking, obesity)
Concomitant drug therapy
Pharmacokinetic factors perturbing the concentration-response relation:
Assay insensitivity
Active metabolites
Non-plasma site of action
Delayed effect
Pharmacodynamic factors:
Interindividual variability in "sensitivity"
Greater or smaller response
Absent or present response
Qualitatively altered response

with toxicity, appropriate dosing intervals.

This approach assumes some correlation between (measurable) drug concentrations and drug effects. Concentrations associated with efficacy obviously vary with the definition adopted for efficacy (e.g. improvement in symptoms vs. prolonged survival for vasodilators in congestive heart failure; abolition of all PVCs vs. inability to induce sustained VT for antiarrhythmics). Pharmacokinetic factors which may perturb the relationship between concentration and efficacy have been intensively studied and include assay insensitivity, generation of active metabolites, important effector sites not in equilibrium with plasma, and delayed effects such as bone marrow depression produced by antineoplastics well after drug has been completely eliminated (Table I). Similarly, not all adverse effects are related to plasma concentrations. Some adverse drug effects will occur predictably at high plasma concentrations: AV nodal conduction disturbances with high concentrations of digitalis are an example. Other adverse drug effects tend to occur at higher concentrations but only in selected patient subsets or under certain clinical

conditions: Torsades de Pointes developing during antiarrhythmic drug therapy in individuals who are hypokalemic as a consequence of diuretic therapy is an example. Third, certain adverse drug reactions are, at this time, classified as "idiosyncratic", a term which serves to underline our own ignorance of the mechanisms involved but which also indicates a failure to correlate with any known drug concentration: an example is pulmonary fibrosis during amiodarone.

Pharmacokinetic Parameters: Definitions

A number of pharmacokinetic parameters can be derived from drug disposition studies. Clearance refers to the amount of drug removed from plasma per unit time. A number of volume of distribution terms can be calculated; the most commonly used is the central volume of distribution which is, approximately, that volume within in which the drug is distributed immediately following a bolus intravenous injection. For most drugs, the central volume of distribution is smaller than the total volume of distribution, implying that drug distributes to peripheral sites. This distribution process can occasionally be quite slow and, if an effector site is located in peripheral tissues, the corresponding onset of drug action can also be slow. Elimination half-life is perhaps the most familiar pharmacokinetic parameter. The use of the term "half-life" implies that elimination is an exponential process; that is, 50% of the process is completed in one half-life, 50% of the remainder (i.e. a total of 75%) in another half-life, 87.5% in a third half-life, etc.).

Pharmacokinetic Parameters: Implications

The central volume of distribution is a major determinant of loading dose; in situations in which the central volume of distribution is reduced, a smaller loading dose will attain the same concentrations following an intravenous bolus dose while use of ordinary doses will achieve higher than usual concentrations.

It is commonly thought that prolongation of elimination half-life mandates the use of lower dosages. This is usually true, but only because decreased clearance, which is a major determinant of plasma concentration during steady-state (Cp_{ss}), also increases elimination half-life. Cp_{ss} is a function of dose per unit time (D), bioavailability (f), and clearance (Cl):

$$Cp_{ss} = f^*D/Cl$$

Elimination half-life not only varies inversely as clearance but also directly as volume of distribution, so the magnitude of changes in dosing should not be

guided by the magnitude of changes in elimination half-life, but by those in clearance. Elimination half-life determines not only the time-course of elimination as described above but also the time-course of drug accumulation to steady-state: 50% of steady-state values will be achieved in one half-life, 75% in two half-lives, 87.5% in 3 half-lives, etc. Therefore, elimination of a drug is near-complete 4-5 elimination half-lives after a last dose is given and steady-state conditions are near-complete 4-5 elimination half-lives after the initiation of a chronic drug regimen. Moreover, it is elimination half-life, in conjunction with the "width" of the therapeutic window which determines the optimum frequency of drug administration. For drugs with very short elimination half-lives, frequent dosing is only required if there is also a narrow therapeutic margin. Beta-blockers, for example, are frequently eliminated fairly rapidly but can be administered infrequently because of their wide therapeutic margins.

Steady-State. A concept which frequently creates some difficulty is pharmacokinetic "steady-state". Steady-state conditions are assumed to prevail when, during chronic drug therapy, an equilibrium exists among plasma concentrations of drug, tissue concentrations of drug, and plasma and tissue concentrations of drug metabolites. Rapid attainment of "therapeutic" plasma concentrations of drug through the use of a loading dose strategy does not hasten the time to development of steady-state conditions (4-5 elimination half-lives). Obviously, when the clinical indication is sufficiently urgent and plasma concentrations are known to correlate roughly with drug effect, a loading dose strategy may be appropriate. However, in the absence of an urgent clinical indication, a loading dose strategy merely exposes the patient to potential risk as a result of high plasma concentrations without hastening the development of steady-state. In addition, administration of (frequently parenteral) large loading doses may result in direct or reflex-mediated adverse drug effects which are not present during steady-state (e.g. marked hypotension due to peripheral vasodilation with quinidine or acute heart failure with amiodarone), while neurohumoral changes during chronic drug therapy are absent after acute dosing.

Pharmacokinetics In Congestive Heart Failure

Pharmacokinetic information has been particularly important in the management of cardioactive drugs, since their therapeutic margins are frequently so small. The best studied class of drugs have been the antiarrhythmic agents

and digitalis glycosides since they have generally fairly clear-cut relationships between plasma concentrations and drug effect (both beneficial and undesirable) and therapeutic plasma concentration monitoring is widely available. The pharmacokinetics of digitalis glycosides are generally unaltered by congestive heart failure unless there is concomitant renal disease to perturb digoxin disposition or advanced liver disease which alters digitoxin disposition. Even severe right heart failure does not appear to impair digoxin absorption. On the other hand, congestive heart failure can have a profound impact on antiarrhythmic drug pharmacokinetics. The best studied example is lidocaine. Congestive heart failure reduces lidocaine central volume of distribution (so lower loading doses are necessary) as well as decreasing liver blood flow, the major determinant of lidocaine clearance. Therefore, lidocaine maintenance infusion rates should also be reduced to avoid high concentrations and toxicity. Congestive heart failure does not have a profound impact on the elimination half-life of lidocaine (since elimination half-life varies directly as volume of distribution and inversely as clearance). Therefore, the time to steady-state (4-5 elimination half-lives or 8-10 hours) is unaltered. Similarly, lidocaine plasma concentrations will fall to near undetectable 8-10 hours following continuation of therapy. Other antiarrhythmics whose clearance is reduced by heart failure include quinidine, disopyramide, and flecainide. The latter two are a particular problem because they may also exacerbate heart failure. Therefore, the use of usual doses in heart failure may lead to high concentrations, further exacerbating the heart failure and further impairing drug elimination. On the other hand, the disposition kinetics of tocainide, procainamide, and encainide do not appear to be altered by heart failure. No data are available on the impact of congestive heart failure on amiodarone disposition, although the drug is generally very well tolerated by patients with congestive heart failure.

Active Metabolites. For some drugs, biotransformation to active metabolites can occur and may confound interpretation of the relationship between parent plasma drug concentrations and effect. Generation of potent active metabolites occurs during therapy with procainamide, encainide, propafenone, and enalapril. In the case of the former three, biotransformation is dependent in part on genetically-determined activity of specific oxidizing (encainide, propafenone) or conjugating (procainamide) hepatic enzymes, while the hepatic de-esterification of enalapril to enalaprilat (MK422) does not at this time appear to be

polymodal. Congestive heart failure was associated with considerable reduction of enalapril clearance compared to patients without heart failure but with hypertension (0.7 L/min vs 2.6 L/min) as well as prolongation of apparent elimination half-life of enalaprilat by approximately 40%. Peak antihypertensive effects correlated with peak serum concentrations of enalaprilat but not with those of enalapril, and inhibition of angiotensin converting enzyme activity persisted long after elimination of enalapril. These data indicate that the duration of enalapril effect may be prolonged in congestive heart failure due to impaired biotransformation to active metabolite; these data also support the idea of administering enalapril once daily in these patients as opposed to twice daily in hypertensives.

Amrinone/Milrinone. Differences in pharmacokinetics between normal individuals and those with congestive heart failure have also been documented for amrinone and milrinone. For both agents, clearance was reduced and elimination half-life prolonged by congestive heart failure. Moreover, in the case of milrinone, hemodynamic changes after a range of intravenous bolus doses from 12.5 to 75 μg/kg were similar, while heart rate increased significantly after the highest dose. Thus, the pharmacokinetic data suggest a possible threshold dose or concentration beyond which no additive benefit is obtained but which may increase the risk of adverse effects. Moreover, the concept of steady-state with respect to uptake of drug to intracellular sites of action may be particularly relevant to these agents, confounding interpretation of data obtained after acute intravenous dosing.

Furosemide. It is recognized that the efficacy of oral furosemide is diminished in congestive heart failure, but the widely cited explanation, decreased absorption, is probably not responsible. In fact, furosemide is generally poorly bioavailable (40%) but bioavailability in heart failure is unaltered; however, absorption is delayed and peak concentrations (which are a major determinant of drug effect) are reduced. Moreover, furosemide is also a good example of a drug which much reach extra-plasma sites prior to exerting its full effect, being taken up by an organic acid transport mechanism into the urine.

Drug Interactions. Polypharmacy is common in the management of a complex illness such as congestive heart failure. There is a high potential for adverse drug interactions in these patients. Plasma digoxin concentrations will be elevated and toxicity ensue with co-administration of quinidine or amiodarone.

Diuretic-induced hypokalemia may potentiate repolarization prolongation by quinidine-like agents and appears to increase the risk of Torsades de Pointes. Abnormalities in potassium homeostasis can also alter response to digitalis: high concentrations of potassium will decrease digitalis binding to Na-K ATPase and reduce effect. On the other hand, hypokalemia is well known to potentiate digitalis toxicity.

PHARMACODYNAMIC FACTORS

Even in the face of identical plasma and tissue concentrations of drugs and their metabolites, response may vary. This may take the form of quantitatively different responses (i.e. greater or lesser or absent drug effect) or qualitatively different responses (i.e. a response in one group of patients not seen in another). In general, the reasons for such variability in response relates to often poorly-understood host factors which impact on drug action, such as electrolyte abnormalities, changes in receptor density or function, altered neurohormonal status, etc. Congestive heart failure is a complex syndrome reflecting interplay between the peripheral vasculature, the failing heart, and neurohumoral compensatory mechanisms. The drugs used in the management of this illness frequently produce completely different effects in this population compared to those observed in normal volunteers. It has been proposed that studies of antiarrhythmic drug effects in normal volunteers should be abandoned since such work exposes individuals to risk with no obvious endpoint and no obvious benefit. A similar argument can be mounted in the evaluation of new drug therapies in patients with congestive heart failure.

Qualitatively Altered Response To Drugs

New classes of drugs, including vasodilators and new inotropic agents, have become available for the management of patients with congestive heart failure. Not only have these drugs offered a wider range of options in the management of these patients, they have also pointed out fundamental homeostatic abnormalities in these individuals. In pharmacodynamic terms, the relationship between drug concentration and resultant effect can be modulated by a number of factors in congestive heart failure. For example, hemodynamic response to converting enzyme inhibitor therapy in patients with severe heart failure is variable and qualitatively different from that seen in normals. It is now recognized that hypotension complicating initial therapy is highly dependent on

pre-therapy serum sodium. Moreover, severe hyponatremia also appears to identify patients who are most likely to benefit from this form of vasodilator therapy. Thus, extensive renin-angiotensin activation identifies a group, not only at risk for hypotension but also with a greater chance of both clinical and perhaps prognostic improvement. The problems of tolerance to heart failure therapy and rebound can also be viewed in pharmacodynamic terms. The use of the term tolerance assumes that drug concentrations remain constant but effect declines. A variety of mechanisms have been proposed ranging from beta-receptor down regulation by beta-agonists to progression of underlying heart disease. Administration of vasodilator drugs results in a range of opposing "compensatory" neurohumoral phenomena including reflex vasoconstriction. Removal of vasodilator therapy may therefore result in rebound worsening of symptoms. Re-distribution of blood flow, particularly to the kidneys, may occur during vasodilator therapy in patients with heart failure, an effect opposite to that seen in "normal" individuals. Thus response to a given drug concentration may be not only quantitatively but qualitatively different in patients with heart failure.

Heart Failure As A Risk Factor For Adverse Drug Reactions

Patients with impaired left ventricular performance appear to be at risk for two complications of antiarrhythmic drug therapy, exacerbation of congestive heart failure and aggravation of arrhythmias. As described above, pharmacokinetic factors may result in higher plasma concentrations of certain drugs in patients with congestive heart failure. Development of congestive heart failure during antiarrhythmic therapy reflects an interplay between (usually but not always) elevated plasma concentrations and host factors since it is largely confined to patients whose left ventricular performance is already impaired.

Arrhythmia aggravation by antiarrhythmic drugs appears to take two major forms: that related to marked QT prolongation and Torsades de Pointes, and that related to development of or worsening of sustained ventricular tachycardia, particularly by drugs of the encainide or flecainide type. In the former group, a relationship to impaired left ventricular performance does not appear to be present except insofar as diuretic-induced hypokalemia appears to be a potent exacerbating factors. On the other hand, in the latter type, the presence of impaired left ventricular performance is a powerful determinant of

the development of this adverse drug effect. Specifically, patients with a history of large transmural myocardial infarctions and sustained ventricular tachycardia appear to be at particular risk (up to 20%) during therapy with high dosages of drugs of the encainide or flecainide type. For flecainide, this adverse drug effect appears to be particularly common at plasma concentrations above 1000 ng/ml, while plasma concentration monitoring guidelines have not yet been established for encainide and its major active metabolites. Aggravation of arrhythmias is also a concern during therapy with drugs with direct positive inotropic effects such as catecholamines, amrinone and milrinone. On the other hand, very limited data suggests that enalapril may actually reduce the incidence of ventricular arrhythmias.

SUMMARY

Response to drug therapy can be conveniently regarded as a function of both pharmacokinetic and pharmacodynamic factors. Congestive heart failure can profoundly alter drug disposition. Moreover, drug therapy in patients with congestive heart failure appears to carry a higher risk of some adverse reactions. In addition, the neurohumoral compensatory mechanisms in severe congestive heart failure are so extensive that the response to some drugs is not only quantitatively different but qualitatively different from that observed in normal individuals. Consideration of both pharmacokinetic and pharmacodynamic factors may permit evolution of safer therapeutic strategies in these very ill patients.

SUGGESTED READING:

1. Woosley, R.L., Echt, D.S., and Roden, D.M.: Effects of congestive heart failure on the pharmacokinetics and pharmacodynamics of antiarrhythmic agents. Am. J. Cardiol. 1986;57:25B-33B.
2. Gomez, H.J., Cirillo, V.J., and Irvin, J.D.: Enalapril: A review of human pharmacology. Drugs 1985;30:13-24.
3. Edelson, J., Stroshane, R., Benziger, D.P., Cody, R., Benotti, J., Hood, W.B., Jr., Chatterjee, K., Luczkowec, C., Krebs, C., and Schwartz, R.: Pharmacokinetics of the bipyridines amrinone and milrinone. Circulation 1986;73SIII:145-152.
4. Brater, D.C.: Disposition and response to bumetanide and furosemide. Am. J. Cardiol. 1986;57:20A-25A.
5. Packer, M., and LeJemtel, T.H.: Physiologic and pharmacologic determinants of vasodilator response: A conceptual framework for rational drug therapy for chronic heart failure. Prog. Cardiovasc. Dis. 1982;24:275-292.

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STATUS OF VASODILATORS FOR HEART FAILURE

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The era of vasodilator therapy for heart failure was ushered in by the seminal observation that drugs that act to relax vascular smooth muscle in the peripheral vasculature are capable of profoundly improving the performance of the damaged left ventricle. These initial studies were carried out with phentolamine (1), an alpha adrenoceptor blocker, and sodium nitroprusside (2), a direct-acting vasodilator. Soon thereafter it was demonstrated that nitrates (3), hydralazine (4), and prazosin (5) also exert a favorable acute effect on left ventricular performance. Thus, it soon became apparent that all vasodilator drugs, by virtue of reducing aortic impedance, could improve ventricular emptying and raise stroke volume in the setting of heart failure (6).

Once the acute effect of these drugs became well-understood, the following issues remained to be explored regarding the effect of vasodilators in the treatment of chronic heart failure:

1. Is the vasodilator effect sustained during chronic therapy?
2. Is the vascular site of action of the drug important in determining its clinical effect?
3. Is the mechanism of action of the drug important in determining its clinical effect?
4. Does chronic administration favorably affect exercise tolerance, quality of life, or mortality?
5. Does the etiology of heart failure influence the therapeutic response to these drugs?

Although none of these issues has been entirely resolved, considerable progress has been made toward providing answers. We shall consider each of these questions in turn.

Is the vasodilator effect sustained?

Proof of maintained vascular responsiveness to chronically administered vasodilator drugs is more difficult in heart failure than in hypertension, because the therapeutic response is more difficult to quantitate. Whereas in hypertension the blood pressure serves as an end-point for drug response, in patients with heart failure vasodilator drugs may increase cardiac output and have little effect on arterial pressure. Thus, invasive monitoring of cardiac function has become the standard means of assessing vascular response in this syndrome. Furthermore, the design of studies to detect any tolerance is made difficult by the variables of pharmacokinetics, instability of baseline hemodynamic measurements, and uncertainty regarding the appropriate interval between drug doses.

Data accumulated to date suggests that intravenously-infused nitroglycerin and nitroprusside maintain at least some of their effect during prolonged administration and that orally administered vasodilators exhibit a varying degree of so-called tolerance during prolonged intermittent administration. Prazosin appears to be the most prone to lose its vascular effect on repeated dosing (7) (mechanism unknown), whereas nitrates may lose some of their vascular action, hydralazine may exhibit a modest loss in some patients, and the converting enzyme inhibitors appear to show little evidence of tolerance.

Is the vascular site of action of the drug important?

Vasodilator drugs may act on large arteries (compliance), arterioles (resistance) and veins (capacitance). The hemodynamic effects of action on these various sites are quite different. An

increase in compliance and reduction in resistance will increase cardiac output, whereas an increase in capacitance will reduce cardiac filling pressure (8). Thus, the acute response to a vasodilator drug will be very dependent on whether the drug has a venous effect (e.g. nitrates), a relatively pure arterial effect (e.g. hydralazine), or a more balanced action (e.g. converting enzyme inhibitors).

Whether these vascular sites of action are critical to the chronic response to these drugs is not clear. Conventional wisdom suggests that a balanced action which produces a more favorable acute change in hemodynamics is the preferable profile. This has led to clinical preference for drug regimens including nitrates (hydralazine and isosorbide dinitrate) or ACE inhibitors (captopril) for vasodilator management of heart failure.

Is the mechanism of action of the drug important?

We now have available vasodilator drugs which can act by a variety of mechanisms. These include the so-called direct-acting smooth muscle relaxants (nitrates, nitroprusside, hydralazine); drugs that interfere with the sympathetic nervous system (alpha blockers, post-synaptic and pre-synaptic inhibitors of norepinephrine release, centrally acting antiadrenergics); drugs that interfere with angiotensin II effect (receptor blockers, ACE inhibitors, renin blockers); vasopressin receptor antagonists, and calcium channel antagonists (dihydropyridines, verapamil, diltiazem). Each of these groups of drugs has been studied in patients with heart failure.

The hope has been expressed that an understanding of the mechanism of vasoconstriction in an individual patient might provide the basis for tailoring therapy to counteract the specific vasoconstrictor system involved. Such an approach has not yet been validated. Indeed, the use of plasma renin

activity measurements to identify patients who might have a more favorable response to long-term converting enzyme inhibitor therapy has not as yet been rewarding. Further data are needed to continue exploration of this question.

Does chronic administration of vasodilator drugs have a favorable effect on the syndrome of heart failure?

This question has concerned the pharmaceutical industry in recent years because of the need for proof of clinical efficacy in order to market vasodilator drugs for this syndrome. Several studies have provided evidence of efficacy for specific drug regimens. Isosorbide dinitrate has in several trials been shown to prolong exercise tolerance in heart failure when added to digitalis and diuretic therapy (9). Captopril in similar trials has been shown to improve exercise tolerance, relieve symptoms and increase left ventricular ejection fraction (10). The combination of hydralazine and isosorbide dinitrate has been shown in the recently completed V-HeFT trial to increase life expectancy in digoxin-diuretic treated patients (11). Thus, the data base is expanding in support of the use of vasodilators in symptomatic patients with heart failure.

Does etiology of the heart failure influence the therapeutic response?

Most studies of heart failure have included patients with left ventricular dysfunction of diverse etiologies. Although the mechanism of muscle dysfunction may be quite different in ischemic and non-ischemic diseases, the studies to date do not suggest that the hemodynamics or clinical response to vasodilator drugs is much different in heart failure of different causes. Most studies have not been large enough to provide the power to perform statistical analysis of the responses in subsets, but V-HeFT did carry out such an analysis that suggested a similar benefi-

cial effect of hydralazine-isosorbide dinitrate in patients with and without coronary artery disease.

Future Concerns

Much remains to be studied before the place of vasodilator drugs in the therapeutic armamentarium for heart failure can be established. We need to establish which drug or drugs are better for which patient population. We need to establish at which point in the syndrome treatment should be initiated: before symptoms develop or after. We need to determine the place of digitalis and diuretics in the regimen. We need to evaluate various vasodilator regimens separately and in combination. We need to address the problem of sudden death, an often tragic terminal event in this syndrome. We need to more precisely assess quality of life as well as physiologic end-points in evaluating the responses to therapy. These and other issues are likely to occupy the attention of clinicians, investigators, industry, and the Food and Drug Administration for many years to come.

REFERENCES

1. Majid P.A., Sharma B., Taylor S.H. Lancet 2: 720, 1971.
2. Franciosa J.A., Guiha N.H., Limas C.J., Rodriguera E., Cohn J.N. Lancet 1: 650-654, 1972.
3. Franciosa J.A., Mikulic E., Cohn J.N., Jose E., Fabie A. Circulation 50: 1020-1024, 1974.
4. Franciosa J.A., Pierpont G., Cohn J.N. Ann Intern Med 86: 388-393, 1977.
5. Miller R.R., Awan N.A., Maxwell K.S., Mason D.T. N. Engl. J. Med. 297: 303, 1977.
6. Cohn J.N. Circulation 48: 5-8, 1973.
7. Packer M., Meller J., Gorlin R., Herman M.V. Circulation 59: 531, 1979.
8. Cohn J.N., Franciosa J.A. N. Engl. J. Med. 297: 27-31 and 254-258, 1977.

9. Franciosa J.A., Nordstrom L.A., Cohn J.N. JAMA 240: 443-446, 1978.

10. Captopril Multicenter Research Group. J. Am. Coll. Cardiol. 2: 755-763, 1983.

11. Cohn J.N., Archibald D.G., Ziesche S., Franciosa J.A., Harston W.E., Tristani F.E., Dunkman W.B., Jacobs W., Francis G.S., Flohr K.H., Goldman S., Cobb F.R., Shah P.M., Saunders R., Fletcher R.D., Loeb H.S., Hughes V.C., Baker B. New Engl. J. Med. 314: 1547-1552, 1986.

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PERSPECTIVES ON THE USE OF NEW PHOSPHODIESTERASE INHIBITORS IN THE TREATMENT OF CHRONIC CARDIAC FAILURE

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Over the past few years, the potential therapeutic usefulness of a new class of phosphodiesterase (PDE) inhibitors (Table 1) has been investigated in patients with chronic cardiac failure. From the data currently available, one can only conclude that despite acute hemodynamic efficacy characterized by enhanced cardiac output with reduced filling pressure, the benefits of this new class of agents are highly controversial. Some investigators have concluded that these agents may not be effective treatment for patients with severe chronic heart failure, and have noted that short-term gains may occur with long-term detrimental effects on the myocardium (1-4). Other investigators have observed long-term clinical benefits with chronic administration of these agents, but have also pointed out that the clinical improvement produced by the new PDE inhibitors may be viewed as only palliative, since the underlying disease showed evidence of continued progression (5-8).

Table 1. New Orally Active Phosphodiesterases Available for Clinical Investigation in the Treatment of Chronic Heart Failure

Drug	Manufacturer
Milrinone	Sterling Winthrop
Enoximone	Merrel-Dow
CI-914	Warner Lambert
CI-930	Warner Lambert
Pimobendan	Boehringer-Ingelheim

In the present review of the role of the new PDE inhibitors in the treatment of chronic cardiac failure, no attempt will be made to nurture further this controversy relative to the real or imagined dangers or benefits of these agents. Instead, our discussion is directed toward some misconceptions of mechanism of systemic and regional hemodynamic effects of these agents, the incomplete understanding of the disease process itself, especially with regard to the factors which limit exercise capacity at different stages of the disease, and the lack of adequate endpoints to assess serially the course of chronic heart failure and its impact on the patient. Lastly, an exercise protocol, which includes evaluation of submaximal and maximal capacity, will be proposed to overcome some of the limitations we perceive in current stress testing designed to assess the failing circulation.

Papaverine and theophylline are traditional PDE inhibitors which inhibit all three major PDE isoenzymes, I, II and III. The newer agents, such as enoximone, milrinone, and CI-914, exert a more selective and competitive inhibition of PDE Type III (9-12). Their action results in a reduced breakdown of myocardial cAMP which potentiates calcium delivery to the contractile system of the heart, while enhancing vascular relaxation. In view of the rise in myocardial contractility, these compounds have been proposed as positive inotropic agents and are compared in their parenteral form to dobutamine and in their oral form to digitalis glycosides (13-18). However, the inotropic responses to these agents are complex. Whereas the stimulatory response to increased calcium or the catecholamine dobutamine in the myocardium remains substantial in failing hearts, the positive inotropic response to the new PDE inhibitors appears more modest at late stages of heart failure (19). In contrast to their modest inotropic effects, the new PDE inhibitors have potent direct veno- and arteriolar vasodilating properties which are dose related and ultimately prevent administration of higher doses, as patients tend to experience symptoms from excessive reduction in systemic arterial and ventricular filling pressures (20-22). The substantial venous and arterial vasodilation of the new PDE inhibitors provide the major mechanism by which they

improve left ventricular performance (23,24). Their concomitant inotropic action helps explain why they are much better tolerated hemodynamically than pure vasodilator agents for an equal increase in cardiac performance (25). When introduced for clinical investigation, the new PDE inhibitors were presented as prototypes of a new class of non-adrenergic, non-digitalis inotropic agents. With the above considerations in mind, they are now better viewed as inotropic agents with important vasodilating properties (26-28).

The vasodilating properties of the new PDE inhibitors help explain why they increase left ventricular performance without increasing myocardial oxygen requirements (29-32). In contrast, predominant inotropic agents, such as dobutamine, increase contractility to a greater extent without the same degree of preload reduction, and thus, consistently increase myocardial oxygen requirements while improving cardiac performance (31,32). The relative emphasis on the importance of inotropic effects of the PDE inhibitors has led to the ill-conceived notion that the new PDE inhibitors should have a detrimental effect on the myocardium when administered chronically. Indeed, without much experimental or clinical support, it was proposed several years ago that overstimulation of the failing heart by potent inotropic agents would potentially "whip the heart to death" and hasten the

demise of the patient (33,34). In view of their modest inotropic effects, it is doubtful that such a concept, if even correct, should be applied to the new PDE inhibitors. To the contrary, PDE inhibitors, which should be viewed as well-tolerated vasodilators, might prolong life in patients with chronic congestive heart failure, as do hydralazine and nitrates (35).

When concerned with the adverse effects during chronic administration of these agents, it is important to parallel these new PDE inhibitors with the more traditional ones, such a theophylline. It is known that chronic administration of theophylline is well tolerated as long as the plasma level is below 20 mg/L (30,36). Above such plasma level, theophylline therapy is complicated by supraventricular and ventricular arrhythmias, as well as gastrointestinal symptoms such as nausea, vomiting, diarrhea, and non-specific abdominal pain. Similarly, a pro-arrhythmic effect and gastrointestinal complaints are not infrequent events during chronic administration of the new PDE inhibitors, as was observed in the setting of compassionate protocols in patients with severe congestive heart failure. In such patients, the combination of markedly reduced renal function and administation of high doses of the new PDE inhibitors are likely to result in excessively high plasma levels (1,37). For example, the use of enoximone at lower doses is associated with a

reduced frequency of side effects when compared to the initial experience with higher doses (38). Endpoints of efficacy with lower doses remained to be demonstrated in double-blind controlled trials. In addition, some new PDEs seem to have active metabolites which further complicates the pharmacokinetic studies of these compounds (39).

Viewing the new PDE inhibitors as primarily vasodilators rather than positive inotropic agents has important implications for their role in the treatment of chronic cardiac failure (Fig. 1). Over the recent years, it has been established that chronic administration of

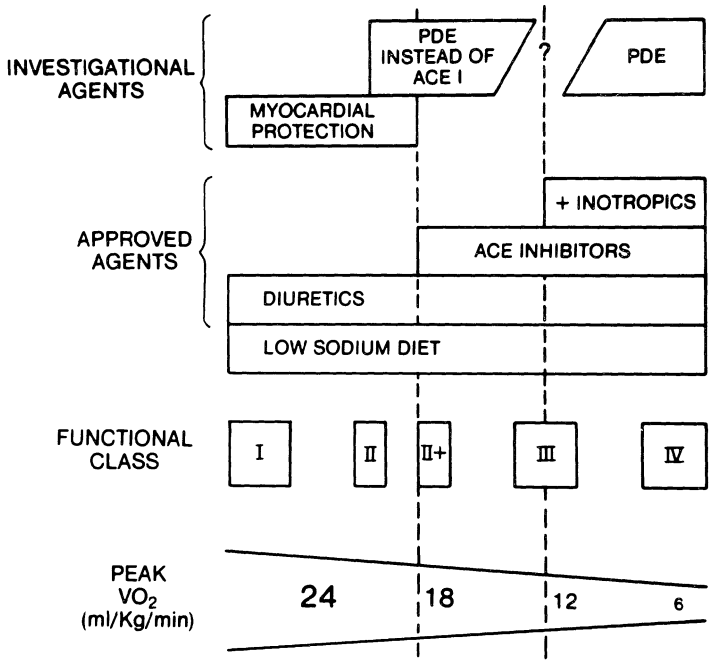

Fig. 1. Therapeutic steps at various stages of chronic heart failure. At a stage of mild to moderate chronic heart failure when the renin angiotensin system is not activated and sodium retention is minimal, angiotensin converting enzyme (ACE) inhibitors could possibly be advantageously replaced by the new phosphodiesterase (PDE) inhibitors. At a more advanced stage of the disease, both pharmacologic interventions may be combined successfully. Pure inotropic agents are mostly beneficial when symptoms and signs of congestion are manifest.

digoxin for the treatment of heart failure is mostly beneficial in patients with evidence of severe congestive heart failure, as evidenced by a third heart sound or pulmonary rales. Patients with left ventricular dysfunction, who do not have the findings of peripheral congestion, do not seem to benefit from chronic use of digitalis (40,41). Similarly, we have noted that although acute administration of dobutamine exerts a greater inotropic effect in patients with less severe disease (42), the improvement in left ventricular performance tends to be greater in patients with more severe disease, suggesting that a reduction in arterial impedance directly or indirectly mediated by dobutamine represented an important contributing mechanism to improved left ventricular performance (42,43). Thus, while a low sodium diet and diuretics should represent the first step in the treatment of chronic heart failure, the second logical step would be to add a vasodilator.

Captopril, an angiotensin converting enzyme (ACE) inhibitor, is approved by the FDA as a vasodilator for

the treatment of heart failure. Its use is certainly indicated when the renin angiotensin system is activated at relatively late stages of the disease, and the clinical results have been extremely encouraging (44,45). However, at an earlier stage of the disease process, when the patient is in a so-called compensated state, the renin angiotensin system may not be activated (46-48). As demonstrated by Cody et al (49), this population of patients can be divided into two subsets: those who are able to excrete sodium normally; and those who are sodium retainers. Although the exact mechanism of avid sodium retention during a compensated stage of heart failure is not well understood, it is generally acknowledged that ACE inhibition promotes sodium excretion. In contrast, there is little pathophysiologic support or clinical experience to support the use of ACE inhibition in patients who are able to excrete sodium normally. These patients are likely to benefit from non-specific vasodilators with persistent activity. Since the new PDE inhibitors are well tolerated, they may represent such an agent. Moreover, the increase in renin activity which often accompanies administration of non-specific vasodilators is not likely to result in water retention, since these patients are able to excrete sodium normally. At this stage of the disease and for reasons that will be discussed with the pathophysiology of exercise, there may

be no indication to combine non-specific vasodilator therapy with chronic ACE inhibition. There may be an added role for ACE inhibitors at an earlier stage in patients who only manifest increased renin-angiotensin activity during periods of stress. This consideration is not well defined. However, at a later stage of the process, when frank decompensation supervenes, the additive effects of the new PDEs with ACE inhibition, like captopril, on cardiac performance and regional blood flow distribution may well explain the clinical benefits noted in open-label trials (50). In others and in our own experience (51), pretreatment with new PDE inhibitors may facilitate administration of captopril in patients who could not tolerate this agent when administered alone. Moreover, at this late stage of the disease, predominant positive inotropic agents may have a growing and necessary role.

The factors which limit capacity to exercise in patients with chronic heart failure may be different during compensated and decompensated stages of the disease. When heart failure is in an early stage or compensated, limitation to exercise performance occurs primarily from deconditioning of the skeletal muscles and, to a lesser extent, by the inability of the heart to pump blood appropriately during exercise. Inadequate vasodilatory capacity of the muscle vasculature or an

abnormal skeletal muscle metabolism does not occur early on (52-54). At a more advanced stage of the disease, the heart and its limitation as a pump may no longer be the limiting factor to exercise performance. Rather, the peripheral vasculature cannot vasodilate adequately during exercise to take full advantage of the increase in cardiac output (54).

When considering the factors which limit exercise, it is important to distinguish between left ventricular diastolic and systolic dysfunction as a cause of heart failure. In the former, due to the inability of the heart to fill, which results in excessive rise in left ventricular filling pressure and pulmonary stiffness, patients are likely to stop exercising prematurely, due to dyspnea, before reaching anaerobic threshold, femoral vein oxygen desaturation, and lactate production. With systolic dysfunction, cardiac output may be inadequate. Patients are more likely to reach anaerobic threshold, almost full femoral vein oxygen desaturation and lactate production (55). Inadequate perfusion of the respiratory muscle, which represents a substantial percentage of the now limited cardiac output, may provide another basis for dyspnea (56,57).

Such difference in the factors which may limit the capacity to exercise in patients with chronic heart failure at various stages of disease has important thera-

peutic implications. Indeed, one of the most important therapeutic goals in patients with chronic heart failure is to allow them to sustain their daily activities without undue discomfort. At a compensated stage of the disease, this may be achieved by decreasing the sensation of dyspnea or fatigue during exercise, allowing the increased activity to result in a physical conditioning effect on the skeletal muscles. When such an effect has occurred, it is unlikely that combination therapy can result in further improvement. On the contrary, reducing the perfusion pressure of the skeletal muscles during exercise by excessive vasodilatory therapy may compromise the oxygen delivery to the skeletal muscles. In contrast, at a more advanced stage of the disease, when the peripheral circulation is markedly abnormal, one might gain by combining increased sodium excretion induced by chronic ACE inhibition, and skeletal muscle vasodilation with non-specific vasodilators (50). This would be most beneficial at submaximal workload.

Improvement in exercise capacity at a late stage of the disease is determined by the results of two different forces: the therapeutic intervention which tends to improve the status of the peripheral circulation, thus enhancing exercise capacity; and the natural deterioration of the disease which keeps on reducing the activity of the patients (58). At a compensated stage of the

disease, the potential changes in exercise capacity may be modified by the therapeutic intervention as long as the disease does not progress. When the disease progresses substantially over the course of a few months, which is generally the case, benefits are readily lost. In contrast, it is also difficult to show an improvement in exercise capacity in patients who, to start with, only have modest limitation in exercise capacity.

Since the therapeutic endpoints in the treatment of congestive heart failure have been thoroughly reviewed by Dr. Sonnenblick, we will not discuss the advantages and drawbacks of exercise testing when compared to other endpoints, such as quality of life or serial evaluation of left ventricular function. Rather, the limitation of maximal oxygen uptake (VO_2 max) as a therapeutic endpoint will be briefly pointed out and an alternative exercise protocol will be proposed. VO_2 max, which is defined by the failure of oxygen uptake to increase despite an increase in workload, is not easily measured in patients with chronic heart failure. Patients may agree to undergo such grueling tests once or twice, but in our experience, are not likely to perform such tests every three weeks. Moreover, VO_2 max which was initially proposed as an index of endurance in cross-country skiers and long-distance runners, has not been shown to predict the sustained performance of athletes (59). Rather, the

sustained running speed which yields a blood lactate concentration between 3 and 5 mM/L is a much better index of stable metabolic state and exercise capacity (60). Thus, when concerned with endurance, which is the centrally important index of exercise capacity for patients as well as athletes, VO_2 max is not only an insensitive criteria by which to measure exercise capacity, but is difficult to measure and an inadequate endpoint.

Accordingly, our current exercise protocol for serial evaluation of patients with chronic heart failure includes two phases. For the first six minutes, the load is submaximal and kept constant. The submaximal load is determined according to the VO_2 max of the patient and corresponds to an oxygen uptake equivalent to 70-75% of the VO_2 max. The following prescription is utilized.

1. Patients in NYHA functional class IV walk at 1 mph at 0^{o} slope.
2. Patients in NYHA functional class III walk at 2 mph at 3.5^{o} slope.
3. Patients in NYHA functional class II walk at 2 mph at 7^{o} slope.

Peripheral venous lactate concentrations are measured at 2, 4 and 6 minutes. The steady-state blood level of lactate is used as an index of the contribution of the anaerobic source of energy to achieve that submaximal

load. Immediately after completion of the submaximal load, the protocol is changed to a ramp with increments in workload following the Naughton protocol (61) every 30 seconds so that patients reach a peak VO_2 within the next few minutes. The entire test lasts less than 10 minutes which, in our opinion, is important since patient motivation and interest usually decreases with the length of the test. We are presently extending our validation of such a protocol. In particular, changes in peripheral vein lactate and skeletal muscle oxygen delivery and utilization are being correlated prior to and after therapeutic intervention. Skeletal muscle oxygen delivery and utilization are derived from measurement of skeletal muscle blood flow by xenon washout technique and determinations of radial artery and femoral vein oxygen content (62).

In summary, the role of the new PDE inhibitors has not yet been established in the treatment of chronic heart failure. Since their predominant mode of action is to reduce cardiac preload and afterload, their future is similar to that of non-specific vasodilators which have not yet been approved for the treatment of chronic heart failure. The new PDE inhibitors are well tolerated hemodynamically and do not appear to negatively influence the trajectory of the disease. As is the case with other agents, their evaluation at endstage of heart failure is

complicated by the rapid and spontaneous deterioration of the disease. They may be beneficial at an earlier stage of disease, mainly when the renin angiotensin system is not activated and sodium retention is not present. To facilitate this evaluation, a submaximal exercise test protocol has been developed which helps assess endurance capacity in exercise performance which first principles would support as central to patient wellbeing.

REFERENCES

1. Packer, M., Medina, N., Yushak, M. Circulation 70: 1038-47, 1984.
2. Uretsky, B.F., Generalovitch, T., Verbalis, J.G., Valdes, A.M., Reddy, P.S. J. Am. Coll. Cardiol. 5: 1414-22, 1985.
3. Shah, P.K., Amin, D.K., Hulse, S., Shellock, F., Swan, H.J.C. Circulation 71: 326-31, 1985.
4. Rubin, S.A., Tabak, L. J. Am. Coll. Cardiol. 5: 1422-27, 1985.
5. Maskin, C.S., Forman, R., Klein, N.A., Sonnenblick, E.H., LeJemtel, T.H. Am. J. Med. 72: 113-18, 1982.
6. Likoff, J., Weber, K.T., Andrew, V., et al. J. Am. Coll. Cardiol. 3: 1282-90, 1984.
7. Simonton, C.S., Chatterjee, K., Cody, R.J. J. Am. Coll. Cardiol. 6: 453-59, 1985.
8. Baim, D.S., Colucci, W.S., Monrad, S.E., et al. J. Am. Coll. Cardiol. 7: 661-70, 1986.
9. Weishaar, R., Quade, M., Boyd, D. et al. Drug Develop. Res. 3: 517-34, 1983.
10. Bristol, J.A., Sircar, I., Moos, W.H., Evans, D.B., Weishaar, R.E. J. Med. & Chem. 27: 1099-1101, 1984.
11. Endoh, M., Yamashita, S., Taira, N. J. Pharmacol. Exp. Ther. 221: 775-83, 1982.
12. Weishaar, R., Quade, M., Schenden, J., et al. J. Pharmacol. Exp. Ther. (in press).
13. Benotti, J., Grossman W., Braunwald, E., et al. N. Engl. J. Med. 299: 1373-77, 1978.
14. LeJemtel, T., Keung, E., Sonnenblick, E., et al. Circulation 59: 1098-1104, 1979.
15. Klein, N., Siskind, S., Frishman, W., et al. Am. J. Cardiol. 48: 170-75, 1981.
16. Amin, D.K., Shah, P.K., Shellock, F.G., et al. Am. Heart J. 109: 91-8, 1985.

17. Benotti, J.R., McCue, J.E., Alpert, J.S. Am. J. Cardiol. 56: 19B-24B, 1985.
18. Jessup Likoff, M., Ulrich, S., Hakki AH, Iskandrian, A.S. Am. J. Cardiol. 57: 1328-34, 1986.
19. Brown, L., Lorenz, B., Erdman, E. Cardiovasc. Res. 20: 516-20, 1986.
20. Alousi, A., Helatosky, A. Fed. Proc. 39: 855, 1980.
21. Meisheri, K., Palmer, R., Van Bresman, C. Eur. J. Pharmacol. 61: 159-65, 1980.
22. Cody, R.J., Muller, F.B., Kubo, S.H., et al. Circulation 73: 124-29, 1986.
23. Strain, J., Grose, R., Maskin, C.S., LeJemtel, T.H. Am. Heart J. 110: 91-6, 1985.
24. Sonnenblick, E.H., Grose, R., Strain, J., et al. Circulation 73 (Suppl III): 162-66, 1986.
25. The Milrinone Investigations and their Associates. Am. J. Cardiol. (in press).
26. Konstam, M.A., Cohen, S.R., Werland, D.S., et al. Am. J. Cardiol. 57: 242-48, 1986.
27. Colucci, W.S., Wright, R.F., Braunwald, E. N. Engl. J. Med. 314: 349-58, 1986.
28. Jaski, B.E., Fifer, M.A., Wright, K.F., Braunwald, E., Colucci, W.S. J. Clin. Invest. 75: 643-49, 1985.
29. Jentzer, J.H., LeJemtel, T.H., Sonnenblick, E.H., Kirk, E.S. Am. J. Cardiol. 48: 75-83, 1981.
30. Benotti, J., Grossman, W., Braunwald, E., et al. Circulation 62: 28-34, 1980.
31. Monrad, E.S., Baim, D.S., Smith, H.S., et al. Circulation 71: 972-79, 1985.
32. Grose, R., Strain, J., Greenberg, M., et al. J. Am. Coll. Cardiol. 7: 1107-13, 1986.
33. Katz, A.M. Circulation 47: 1076-82, 1973.
34. Katz, A.M. N. Engl. J. Med. 299: 1409-10, 1978.
35. Cohn, J.N., Archibald, D.G., Ziesche, S., et al. N. Engl. J. Med. 314: 1542-47, 1986.
36. Piafsky, K.M., Ogilvie, R.I. N. Engl. J. Med. 292: 1218-22, 1975.
37. Kinney, E.L., Carlin, B., Ballard, J., et al. J. Clin. Pharmacol. 22: 433-39, 1982.
38. Weber, K.T., Janicki, J.S., Jain, M.C. Am. J. Cardiol. 58: 589-95, 1986
39. Mancini, D., Sonnenblick, E.H., Latts, J.R., et al. Circulation 70 (4): II-307, 1984.
40. Lee, D.C.S., Johnson, R.A., Bingham, J.B., et al. N. Engl. J. Med. 306: 699-705, 1982.
41. Arnold, S.B., Byrd, R.C., Meister, W., et al. N. Engl. J. Med. 303: 1443-48, 1980.
42. LeJemtel, T.H., Keren, G., Reis, D., Sonnenblick, E.H. J. Cardiovasc. Pharmacol. (in press).
43. Sonnenblick, E.H., Frishman, W.H., LeJemtel, T.H. N. Engl. J. Med. 300: 17-22, 1979.
44. Captopril Multicenter Research Group. J. Am. Coll.

Cardiol. 2: 755-63, 1983.
45. Sharpe, D.N., Murphy, J., Coxen, R., Hannan, S.F. Circulation 70: 271-78, 1984.
46. Watkins, L., Burton, J.A., Haber, E., et al. J. Clin. Invest. 57: 1606-17, 1976.
47. Dzau, V.J., Colucci, W.S., Hollenberg, N.K., Williams, G.H. Circulation 63: 645-51, 1981.
48. Mettauer, B., Rouleau, J.L., Bichet, D., et al. Circulation 73: 492-502, 1986.
49. Cody, R.J., Covit, A.B., Schaer, G.L., et al. J. Clin. Invest. 77: 1441-52, 1986.
50. LeJemtel, T.H., Maskin, C.S., Mancini, D., et al. Circulation 64: 364-69, 1985.
51. LeJemtel, T.H., Gumbardo, D., Chadwick, B., et al. Circulation 73 (Suppl III): 213-18, 1986.
52. Zelis, R., Flaim, S. Prog. Cardiovasc. Dis. 24: 437-59, 1982.
53. Wilson, J.R., Fink, L., Maris, J., et al. Circulation 71: 57-62, 1985.
54. LeJemtel, T.H., Maskin, C.S., Lucido, D., Chadwick, B. Circulation 74: 245-51, 1986.
55. LeJemtel, T.H., Maskin, C.S., Chadwick, B., Sinoway, L. J. Am. Coll. Cardiol. 1 (2): 662, 1983.
56. Aubier, M., Trippenbach, T., Roussos, C. J. Appl. Physiol. 51 (2): 499-508, 1985
57. Roussos, C. Lung 160: 59-84, 1982.
58. Convert, G., Delaye, J., Beaune, J., et al. Arch. Mal Coeur 3: 227-37, 1980.
59. Davis, J.A. Med. Sci. Sports Exer. 17: 6-18, 1985.
60. Brooks, G.A. Med. Sci. Sports Exer. 17: 22-31, 1985.
61. Patterson, J.A., Naughton, J., Pietras, R.J., Gunnar, R.M. Am. J. Cardiol. 30: 757-64, 1972.
62. Mancini, D., Davis, L., Wexler, J.P., et al. Circulation 70 (4): II-193, 1984.

16

IS THERE A ROLE FOR BETA-BLOCKERS IN HEART FAILURE PATIENTS?

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INTRODUCTION

On initial reflection, consideration of beta-blockade in the therapy of heart failure (HF) patients seems paradoxical. In most discussions of the therapeutics of congestive heart failure, beta-blockers are listed as contraindicated, given their known negative inotropic potential. The general perception that beta-blockers are contraindicated is adequately supported by clinical anecdotes, in which the administration of beta-blocker therapy (usually intravenously) in patients with acute or subacute and medically uncompensated HF has led to dramatic adverse reactions such as acute pulmonary edema and low output syndrome with hypotension and shock. Thus, the consideration of beta-blockade for therapy of HF patients would appear heretical based on conventional medical wisdom. Nevertheless, standard therapy for HF, while controlling symptoms in the short term, appears to have had little impact on the dismal natural history of the disease (1-4). Given this poor prognosis, the testing of new and unconventional approaches to chronic HF is appropriate. In this regard, it is of interest that despite the obvious danger in administering intravenous and full-dose beta-blocking drugs in acute HF, giving carefully titrated oral doses to patients with medically compensated, chronic HF is gaining increasing clinical and experimental support.

EVIDENCE FOR A ROLE FOR BETA-BLOCKERS IN HEART FAILURE DUE TO CORONARY ARTERY DISEASE

The net effect of beta-blocker therapy in patients with ischemic heart disease and left ventricular dysfunction is difficult to

predict. Beta-blockade may exacerbate HF by decreasing contractility, increasing ventricular volume, and suppressing sympathetic activity which may be an important compensatory mechanism in acute HF. On the other hand, beta-blockade may improve left ventricular function by improving the balance between oxygen demand and supply. Other beneficial effects may also be invoked during chronic beta-blocker therapy (see below).

The most important clinical data relating to a role for beta-blockade in HF associated with coronary artery disease comes from patient subgroups with left ventricular dysfunction included in the large randomized mortality trials of beta-blockers post-infarction (5-8). These trials suggest that beta-blockers provide a substantial mortality benefit even in patients with the most severe left ventricular dysfunction allowed study entry. Moreover, clinical HF was an uncommon complication of therapy even in those with prior mild-to-moderate, compensated HF.

In the Norwegian timolol trial (5,9,10), randomization was carried out within three risk strata. Risk group 1 consisted of patients with a previous infarction, group 2 included patients with a complicated first infarction (i.e., enzymatically large infarction, transient left ventricular failure, or cardiomegaly), and group 3 represented uncomplicated first infarctions. Thus, patients with significant left ventricular dysfunction were contained in groups 1 and 2. Overall, a relative reduction of 39% in cumulative life-table mortality was observed in 1,884 patients entered and followed for 1233 months ($p<0.0003$). No major subgroups were identified for which timolol was not of benefit (10). Relative reductions were also observed in high risk subgroups 1 and 2 for total mortality (19% and 39%) and, especially, sudden death (<24-hour) mortality (31% and 43%) (9). In another analysis, mortality was reduced similarly for those with cardiomegaly (by 33%) and those with normal heart size (by 35%) (10).

In the United States Beta-blocker Heart Attack Trial (BHAT) in 3,837 patients (6,11), a significant reduction in post-infarct mortality (26%) was also observed during a 25-month average follow-up period. Examination of more than 50 subgroups revealed a consistent trend in favor of propranolol in most groups (12). Using the same

three risk group stratifications as the timolol trial, a similar relative impact on mortality was observed in subgroups 1 through 3 (22%, 31%, 27%, respectively) (13).

Further illuminating analyses of the BHAT trial have recently appeared (14,15). On the basis of findings during the initial hospital stay, Furberg et al divided patients into subgroups with mechanical or electrical complications and analyzed the effects of propranolol therapy (14). Signs or symptoms of congestive heart failure, basilar rales, pulmonary edema, cardiogenic shock, and persistent hypotension during hospitalization were considered as mechanical complications. Electrical complications included ventricular tachycardia or fibrillation, complete or partial A-V block, and new onset atrial fibrillation. A total of 22% of patients suffered a mechanical complication, and half of these had an electrical complication as well. In the two risk groups with mechanical complications, propranolol-treated patients experienced an adjusted reduction in relative mortality risk of 43% and 30% respectively, compared with only a 4% reduction observed in those with neither electrical nor mechanical complications and a 57% reduction in those with an electrical complication alone. These results are even more impressive when analyzed as absolute numbers of lives saved. The relative risk reduction in patients with neither electrical nor mechanical complications represents less than half of one life prolonged per 100 patients treated during 25 months. In those with either mechanical and/or electrical problems, between 4 and 6 lives were saved for every 100 patients treated. Of patients who had mechanical problems in BHAT, 25 died instantaneously as compared with 13 receiving propranolol; in addition, fewer non-fatal myocardial infarctions occurred in the active therapy group (15 versus 24).

Recently, Chadda et al have specifically analyzed the effects of propranolol in BHAT patients with HF (15). In BHAT, survivors of acute myocardial infarction with compensated mild or moderate HF, including those on digitalis or diuretics, were eligible for study entry. Patients with shock or overt HF were excluded from enrollment unless they first stabilized. A history of HF either before or during hospitalization was reported overall in 710 patients: 345

(18%) in the propranolol group and 365 (19%) in the placebo group. As expected, prior HF at entry increased the risk of cardiovascular events. Of interest, propranolol had greater relative and absolute effects on fatal and non-fatal events in patients with a history of HF than in those without (Fig. 1).

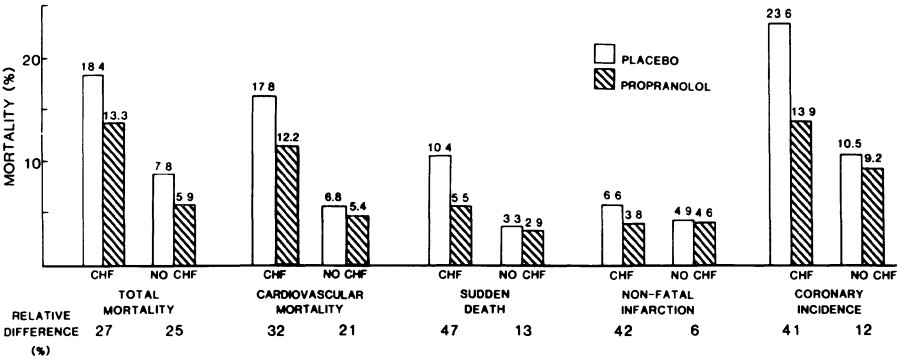

Fig. 1. Total mortality and various cardiovascular endpoints in patients on propranolol (hatched bars) or placebo (open bars) according to congestive HF history. (Reprinted with permission from Chadda et al, Circulation, ref 15 © American Heart Association, 1986).

Propranolol lowered the total cardiovascular mortality rate by 32% (12.2% vs 17.8%) in patients with prior HF and by 21% (5.4% vs 6.8%) in those without. Even more impressively, the incidence of sudden death was reduced 47% (5.5% vs 10.4%) in the HF group vs 13% (2.9% vs 3.3%) in the group without an HF history. Substantial group benefit was also observed in the incidence of non-fatal reinfarction and in total coronary events in the propranolol compared with placebo group. Although percentage reduction in total mortality was about equal in HF (25%) and non-HF patients (25%), the absolute reduction was over 5 deaths per 100 patients treated in the HF group, compared with a reduction of less than 2 deaths in the non-HF group because of the higher risk of death when HF had been present.

Congestive HF was more commonly observed as a complication of propranolol than placebo therapy in those with a history of prior HF, compensated. In all trials, benefits of therapy were observed

in subgroups with the greatest degree of mechanical and electrical dysfunction who were permitted study entry. The absolute benefit, in terms of lives saved per 100 patients treated, was in fact greatest in patients with prior HF. Patients with HF are particularly prone but the incidence was modest and occurred early during therapy (15). Within 30 days of randomization, 4.3% of heart failure patients receiving propranolol experienced recurrent congestion, compared with 1.6% receiving placebo. Thereafter, the curves of cumulative HF recurrence in propranolol and placebo-treated patients were parallel (Fig. 2).

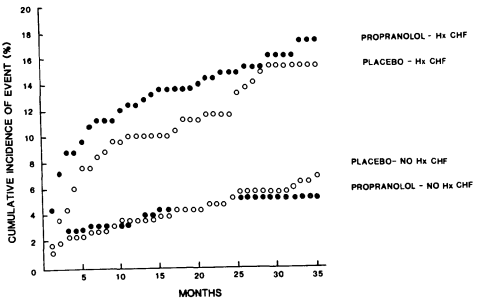

Fig. 2. Incidence of HF in propranolol (closed circles) and placebo (open circles) patients with or without a history of HF. (Reprinted with permission from Chadda et al, Circulation ref. 15, © American Heart Association, 1986).

Propranolol was also tested in heart failure patients in the Norwegian High-risk Propranolol Trial (8,16). Only patients with a history of HF and other high-risk predictors were included. (Patients with shock or pulmonary edema were excluded.) Significantly more patients in the propranolol group were withdrawn because of increased HF during the first few days of therapy, but propranolol led to a 32% overall reduction in mortality (which did not quite achieve significance) and a 50% reduction in sudden death mortality ($p<0.05$). These results are consistent with the subgroup analysis presented above for the larger BHAT trial (15).

In summary, prospective and retrospective analyses of the major post-infarction beta-blocker mortality trials indicate that therapy with these agents is generally safe when carefully administered, even in patients with a history of mild or moderate HF who are clinically to ventricular fibrillation; the substantial reduction (approximately 50%) in sudden death mortality with beta-blocker therapy indicates an antifibrillatory role as one mechanism of its action. The risk of therapy in these patients, in terms of increased incidence of HF, has been surprisingly modest. Increased intolerance to beta-blockade in HF patients usually occurs early during therapy when the patient is under careful observation and can be promptly attended to. Initiation of therapy with low doses of beta-blockers and gradual up-titration may reduce the risk of HF. Thus, careful application of beta-blocker therapy should be strongly considered in these patients to reduce mortality. Additional studies are indicated to evaluate the impact of beta-blocker therapy on cardiovascular function.

BETA-BLOCKERS IN HEART FAILURE DUE TO DILATED CARDIOMYOPATHY

Early studies of beta-blockers in dilated cardiomyopathy.

The feasibility of beta-blocker therapy in dilated cardiomyopathy (DCM) was tested in Sweden in a pilot study in seven patients in 1975 (17). It was postulated that suppression of excessive sinus tachycardia in patients with DCM might have a favorable hemodynamic effect. Low-dose beta-blocker therapy (primarily with metoprolol) was found to be associated with significant clinical improvement, occurring over a period of several months. Subsequent reports (1980, 1983) in an expanding cohort of patients continued to support a beneficial effect (18-20). These results, although greeted with initial skepticism, were of interest because, contrary to the expectation of deterioration based on clinical wisdom, functional class and exercise capacity increased, and tests of myocardial function showed improvement. The initiation of intravenous beta-blocker therapy was noted to be associated with modest decreases in cardiac index (from 2.2 to 1.9 L/min/m^2); however, continued oral therapy was associated with generally good tolerance and improved hemodynamics, with increases in cardiac index, falls in ventricular filling

pressure, and increases in echocardiographic ejection fraction (from an average of 0.34 to 0.50) after six months of therapy (18). Discontinuation of digitalis, decreases in the dose of diuretics, and a return to work were possible in a significant percentage of patients. An associated study of beta-blocker withdrawal in 15 patients provided further evidence for a beneficial effect of therapy (19). Fourteen of these patients showed an increase in heart rate after withdrawal, 13 experienced a fall in echocardiographic ejection fraction, and 6 had clinical exacerbation of HF within two weeks. The survival characteristics of 24 patients treated with beta-blocker therapy were also evaluated and compared to that of an historical control group by the Swedish investigators (21). Mortality, although still substantial, appeared to be improved with the treatment.

In contrast, some other investigators have not observed favorable results from beta-blocker therapy for DCM (22-24). In a placebo-controlled study, Ikram et al tested acebutolol (22). Therapy for one month caused no beneficial effects on symptoms, exercise tolerance, and cardiac size in 17 patients, many of whom had alcoholic DCM. Other negative studies have been reported by Currie et al (23) and Weber et al (24). These studies were also short-term and performed in small, somewhat mixed populations of patients.

Recent, controlled studies in DCM.

Three recent American studies of beta-blockers in DCM have shown promising results (25-27).

In a study at the University of Utah, the ability of beta-blocker therapy to affect survival and functional class in a controlled trial was tested in 50 patients with DCM randomized to low-dose metoprolol (n=25) or standard therapy alone (n=25) (25). The two treatment groups were comparable in baseline characteristics, including left ventricular ejection fraction (which averaged 0.28), New York Heart Association functional class (average class, 2.7), and age (averaging 51 years). The initial dose of metoprolol was 12.5 mg given twice daily. Dosage was increased gradually to 25, then 50 mg twice daily as tolerated. The final average dose was 65 mg per day. Beta-blocker therapy was tolerated initially in 22 (88%) of patients and could be continued in 20 (80%) long-term.

This cohort has now been followed for an average of 48 months since study entry. By the intention to treat method, 8 (32%) have died in the beta-blocker group and 11 (44%) in the conventionally treated group ($p<0.5$) (Fig. 3, left). Evaluating results by the actual-treatment method, mortality is 25% (6/24) for metoprolol treated versus 50% (13/26) for control patients ($p<0.09$) (Fig. 3, right). The latter evaluation is compounded by the possibility that intolerance of initial beta-blocker testing may signify more advanced disease and a worse prognosis.

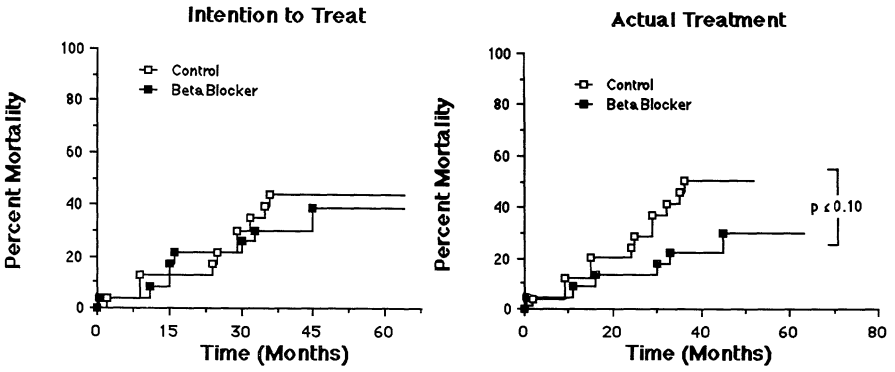

Fig. 3. Life-table curve of mortality in DCM patients in metoprolol (closed squares) and control (open squares) groups. Left: intention-to-treat analysis. Right: actual treatment analysis. (See Anderson et al, ref. 25, for study details).

Functional class was also better in patients actually treated with beta-blocker therapy (New York Heart Association score averaging 2.0 versus 2.7 in untreated patients). Heart rate was modestly reduced (84 to 75 bpm), and treadmill time tended to be better (25).

At Loyola University of Chicago, cardiac functional effects of beta-blocker therapy in DCM were tested (26). The study design included both double-blind, randomized, parallel, and open-label, crossover design portions in a total of 23 patients. Twenty patients received beta-blocker therapy during at least one portion of the study. Metoprolol was begun in a dosage of 6.25 mg once daily and was increased once or twice weekly (in increments of 6.25 to 12.5 mg/day in divided doses) over four to six weeks, as tolerated.

The long dosing phase allowed patients to gradually accommodate to therapy. The dosage goal was 100 mg/day, and the mean final dose achieved was 92 mg of metoprolol per day. Interval evaluations included functional classification, exercise treadmill testing, echocardiography, and radionuclide ventriculography. Metoprolol but not placebo caused reductions in heart rate (from 91 to 75 bpm, $p<0.001$). Highly significant improvements occurred in New York Heart Association functional class (from 2.6 to 1.8, $p<0.001$), exercise tolerance (increasing from 4.4 to 7.9 METS, $p<0.0001$), and ejection fraction (increasing from 0.13 to 0.19, $p<0.02$) (results from double-blind study phase) (Fig. 4). In contrast, placebo therapy was not associated with changes in functional class and exercise MET score ($p<0.001$ for comparison with metoprolol group). Changes between groups in ejection fraction and left ventricular dimension did not achieve significance.

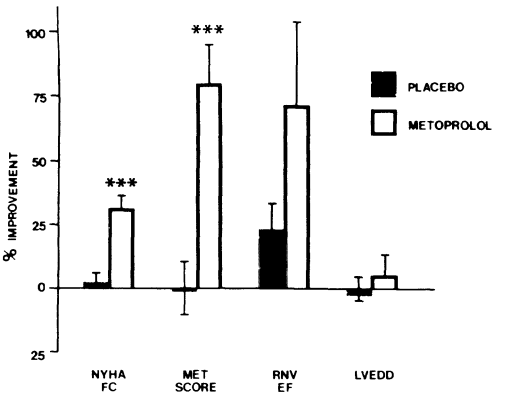

Fig. 4. Change (mean±SD) from baseline in cardiac functional endpoints for DCM patients randomized to placebo (closed bars) and metoprolol (open bars). ***p<0.001. NYHA-FC=New York Heart Association functional class; MET score=treadmill exercise metabolic equivalents achieved; RNV-EF=radionuclide ventriculographic ejection fraction; LVEDD=echocardiographic left ventricular end-diastolic dimension. (Reprinted with permission from Engelmeier et al, Circulation, ref. 26, © American Heart Association, 1985).

Seven of 20 treated patients had an exceptional response to beta-blockade, returning to functional classes 1 or 2, doubling

their exercise tolerance, improving ejection fraction, and decreasing left ventricular diastolic dimension (26). No degree of left ventricular impairment prevented the safe administration of metoprolol, so long as patients were initially clinically stable. In fact, the most favorable responses occurred in those with high resting heart rates and noninvasive indices suggesting advanced left ventricular dysfunction. An especially favorable response was noted in those with symptoms of short duration and in women.

In longer term follow-up (averaging 33 months), symptoms, exercise capacity, and ventricular size and function continue to show improvement after beta-blocker therapy and survival may be improved (26b).

At Stanford University, beta-blocker therapy with either metoprolol or propranolol (mean dose, 90 mg per day) was tried in 17 patients referred for cardiac transplantation (27). Two patients did not tolerate therapy. Two others died within two weeks. However, the other 13 patients tolerated initiation of beta-blockade and were subsequently followed for a mean of 15 months. Clinical improvement was noted in 10 of these. Three patients improved enough to allow their removal from the transplant waiting list. The maximum oxygen uptake during exercise testing increased in nine patients. Exercise duration improved from a mean of 9.5 to 12 minutes. In contrast to the expected response, most patients experienced an increase in double-product during exercise after beta-blockade. This paradoxical response in double product was interpreted as being consistent with up-regulation of beta receptors, resulting in a greater physiologic response to sympathetic nervous system stimulation during physical activity.

Taken together with earlier experience, both positive and negative, these studies affirm that low-dose, carefully titrated beta-blocker therapy is feasible and surprisingly well tolerated in patients with DCM, an unexpected finding. Functional class and survival are not deleteriously affected and, in fact, may improve in certain patient groups, sometimes dramatically. Given the poor prognosis of this disease, even with current therapy, this small but expanding experience from several centers has suggested the need for a more definitive test of beta-blocker therapy in cardiomyopathy.

The multicenter MIDIC trial.

The MIDIC trial (metoprolol in DCM) represents a large, randomized, controlled, multinational trial of beta-blockade in DCM involving several centers, including the United States, and coordinated by Dr. Finn Waagstein, Goteborg, Sweden. MIDIC has been initiated this year (1986) to provide a more definitive test of the hypothesis that beta-blocker therapy may be beneficial in DCM. Patients with documented idiopathic DCM at baseline testing, who have a left ventricular ejection fraction of <0.40 and who show initial tolerance to a test dose of metoprolol (5 mg given twice daily for 2-7 days), are stratified by ejection fraction (at 0.20) and randomly assigned to drug treatment with metoprolol or placebo. Dosing is increased gradually from 10 mg to up to 150 mg per day, in divided doses, as tolerated, over a six-week period. The minimum final dosing goal is 50 mg per day. MIDIC plans to assess the effects of metoprolol and placebo, added to standard therapy, on mortality, morbidity, and cardiac function at rest and during exercise, over a mean follow-up period of two years in a total of 320 patients. Estimating the probability of patients dying or requiring cardiac transplantation to be 30% in two years, a significant difference is expected to be shown for a treatment effect of $\geq$50%. In the event that a favorable trend of lesser degree is apparent after at least one year, the study may be expanded to include about 520 patients. Given its careful design and relatively large numbers, MIDIC is likely to have an important impact in determining the ultimate role of beta-blocker therapy for patients with heart failure caused by DCM.

THE SYMPATHETIC NERVOUS SYSTEM IN HEART FAILURE

The pathophysiology of HF consists of three phases, including that of tissue injury, stimulation of compensatory mechanisms, and, later, progressive functional deterioration. By the time that HF becomes clinically evident, the tissue injury phase is frequently advanced or completed. Clinical interventions are usually begun during the phase of compensation or progressive deterioration. The role of the sympathetic nervous system during these latter phases of

HF has become more evident in recent years (28,29). Understanding these mechanisms may provide a basis for the role of beta-blockade.

The compensatory phase of HF has now been shown to be associated with a hyperadrenergic state characterized by increased levels of circulating catecholamines, particularly norepinephrine (30). Prognosis is strongly related to the level of adrenergic nervous system stimulation. Patient groups with very high, intermediate, and lower risks for mortality were found to be characterized by plasma norepinephrine levels of >800 pg/ml (about 90% two-year mortality), 400-800 pg/ml (75% two-year mortality), and <400 pg/ml (40% mortality), respectively (30). Whether chronically increased circulating norepinephrine levels serve simply as a sensitive marker of the degree of HF or, in addition, may contribute to subsequent functional deterioration is uncertain. However, it is of interest that circulating concentrations of norepinephrine found in patients with HF have been estimated to be <1% of cardiac intrasynaptic concentrations (31,32). Pheochromocytoma provides an interesting disease model characterized by marked elevations in plasma catecholamines in which myocardial degenerative and inflammatory changes are known to occur (31,33).

Excessive catecholamine secretion may cause substantial pathology at the level of the cardiac myocyte (31,34) which may include 1) enhanced sarcolemmal permeability, 2) cellular calcium overload, with myofibrillar hypercontraction and degeneration and mitochondrial calcification, 3) impaired mechanical function, both systolic and diastolic, and beta-adrenergic receptor down-regulation, and 4) life-threatening arrhythmias, which may be provoked by hypokalemia, hypomagnesemia, and increased cellular levels of cyclic AMP and calcium.

Down-regulation of myocardial beta-receptors is a recently demonstrated consequence of chronic catecholamine stimulation (35). Normally, the myocardium is replete with beta-adrenergic receptors (primarily of the beta-1 subtype). These receptors, linked to cyclic AMP and calcium, influence contractility and mediate the response to adrenergic drugs. In the chronically failing heart, beta-1 receptor density is reduced by about two-thirds. The densities of the less numerous beta-2 and alpha-1 receptors, in contrast, are

relatively maintained. Down-regulation of beta-receptors in response to chronic exposure to high norepinephrine levels is explained by uncoupling of the receptors to other components of the adenylate cyclase system and cell membrane and internalization of the receptors within the cell where they are stored or degraded.

As a result of beta-1 receptor down-regulation, the response to beta-agonists, such as isoproterenol, is substantially reduced (by an average of 70%) (35,36). Down-regulation of beta-receptors thus may act to decrease the normal response to adrenergic nervous system stimulation, which may be of physiologic importance during vigorous exercise.

Associated with chronically excessive sympathetic nervous system stimulation in HF, myocardial stores of norepinephrine become depleted and norepinephrine synthesis is inadequate to replenish these stores (31,37). This depletion leads to blunting of the inotropic and chronotropic responses to cardiac sympathetic nerve stimulation (31,38).

In summary, it may be postulated that HF induces compensatory mechanisms which include a reflex increase in sympathethic nervous activity and catecholamine secretion. Adenergic stimulation may be appropriate and beneficial in the short term for acute HF. However, chronic exposure of the myocardium to catecholamines may lead to reduction (down-regulation) of myocardial beta-1 receptor density and direct myocardial catecholamine toxicity, which may contribute to progressive functional deterioration and serious cardiac arrhythmias.

POTENTIALLY BENEFICIAL MECHANISMS OF BETA-BLOCKADE IN HEART FAILURE

Modulation of inappropriate hyperadrenergic stimulation.

By interfering with the vicious cycle of hyperadrenergic stimulation, beta-blockade may be postulated to lead to several favorable functional effects in chronic HF. These include: 1) Up-regulation of beta-1 receptors. Interruption of chronic sympathetic overstimulation may allow beta-receptor density to recover toward normal. Greater responsiveness to appropriate physiologic sympathetic nervous system stimulation may result. 2) Reduction in catecholamine toxicity and improved myocardial energetics. The adverse effects of

catecholamines on membrane function, calcium flux, and myofilament and mitochondrial integrity may be interrupted by beta-blockade, leading to improved cardiac performance. Inappropriate tachycardia, often observed in HF, may be favorably affected as well. 3) Reduction in potentially lethal arrhythmias. Sudden death accounts for about 40%50% of deaths in HF patients. Arrhythmogenic mechanisms associated with direct or indirect effects of catecholamines may be reduced. Reductions in sudden death in patients with HF associated with coronary artery disease have already been demonstrated in clinical trials, as noted above (14,15).

Other potentially beneficial effects of beta-blockers in HF may include reduction in increased vascular resistance associated with increased sympathetic tone (31). Beta-blockers may prevent excessive renin production caused by chronic sympathetic stimulation. Renin induces secretion of angiotensin II, leading to vasoconstriction, and secretion of aldosterone, leading to salt and water retention. Sympathetic stimulation may also promote pituitary secretion of vasopressin, enhancing vascular tone and water retention.

Evidence for a role for beta-blockers in preventing ventricular fibrillation.

In laboratory models of induced ventricular fibrillation (VF), both in the presence and absence of ischemic disease, beta-blockers have shown substantial antifibrillatory activity. The minimal electrical energy required to induce VF when delivered in single or multiple impulses through cardiac electrodes in animal models can be reproducibly determined and is called the VF threshold. Anderson et al (40) measured this threshold before and after coronary ligation in anesthetized (open-chest) dogs before and after dosing with various beta-blockers. In control studies, VF was induced by diastolic current trains of 12±8 mA with normal coronary perfusion and 7≠7 mA with transient regional coronary ischemia (distal left anterior descending coronary zone). Intravenous therapy with five beta-blockers but not saline resulted in substantial increases in VF threshold to levels of 67±30 mA for nonischemic and 42±31 mA for ischemic conditions. The response with timolol is represented in Fig. 5.

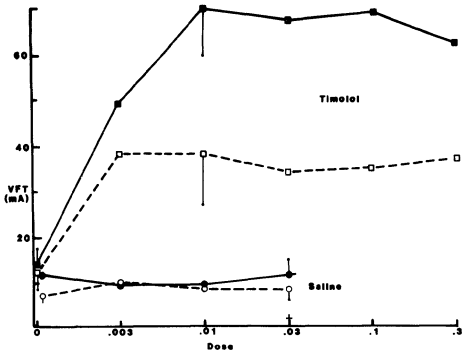

Fig. 5. Effects of timolol (squares; n=10) and saline (circles; n=9) on VF threshold in a canine model. Dose in mg/kg (given IV). (Adapted from Anderson et al, ref. 40). Open symbols, dashed lines = ischemic; closed symbols, solid lines = nonischemic conditions; bars = SEM.

In contrast, nitroglycerin did not demonstrate antifibrillatory effects, and calcium channel blockade (diltiazem) caused more modest effects in this model (41).

The interaction of an aroused sympathetic nervous system and acute ischemia appears to be of particular significance and interruption of adrenergic stimulation to the heart of therapeutic importance for ischemia-induced VF. Schwartz and Stone (42) observed a 65% incidence of VF in a canine coronary ligation model of acute myocardial infarction. After left stellectomy, which substantially interrupts cardiac sympathetic nervous system activity, the incidence of fibrillation was cut in half (to 33%, $p<0.05$).

A sophisticated canine model of sudden cardiac death, simulating in many respects clinical ischemic VF in patients with ventricular dysfunction, has been developed by Patterson, Lucchesi, and coworkers at the University of Michigan (43). In this model, a new ischemic insult (gradual thrombosis of the circumflex artery induced by an electric current) is superimposed on an old, distant infarction (anterior descending zone). By this method, acute ischemia is induced in conscious dogs and monitored by a continuous ambulatory ECG recorder. A mortality of 90% to 100% occurs in untreated

animals within a few hours of current application. Beta-blockers but not standard antiarrhythmics are effective in reducing sudden death in this model. Nadolol in its clinically used racemic form reduced mortality to 37% versus 93% for saline (placebo) (44) (Fig. 6).

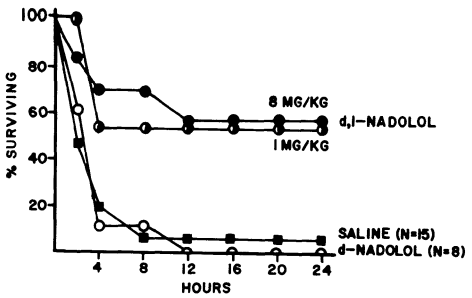

Fig. 6. Effects of d,l- and d-nadolol on survival in a study of canine ischemic VF. Survival was significantly increased at 24 hours after d,l nadolol ($p<0.01$ vs saline). (Reprinted with permission from Patterson et al, ref. 44, 1983).

Efficacy was related to beta-blockade alone because the isomer d-nadolol, a non-beta-antagonist, was ineffective when given alone.

Data from clinical studies, such as the beta-blocker study reviewed above (15), indicate a particularly high risk for VF in patients with ischemic heart disease and left ventricular dysfunction. Goldstein and colleagues have analyzed cardiac symptoms preceding cardiac arrest in patients with coronary heart disease (45,46). This evaluation emphasized the importance of ischemia as the common denominator of sudden cardiac death. Ischemia was felt to represent the initiating mechanism in about 80% of all victims. Among 274 patients resuscitated over a period of ten years, 83% had advanced coronary heart disease; of these, 40% were classified as having acute myocardial infarction, 39% as having another ischemic event, and only 21% as having a primary arrhythmic event. With this clinical model in mind, the results of the experimental studies presented above as well as clinical studies are consistent. Interventions which stabilize the heart against ischemic VF or prevent primary ischemia may be expected to be effective. The highly significant

reductions (about 50%) in sudden death by propranolol in patients with HF is especially noteworthy (15). Revascularization may also play a role in reducing sudden death. The CASS study (47) reported that patients with coronary artery disease and angina treated surgically exhibited decreased numbers of sudden deaths when compared to patients who have not been revascularized. This effect was seen particularly in those with HF and multivessel disease. Thus, medical and surgical interventions which modify ischemia and improve coronary blood flow reduce the potential for VF and appear to be more effective in preventing sudden death than standard antiarrhythmic agents, which have been ineffective in clinical and experimental models to date (43,48,49).

CONCLUSIONS

Despite advances in conventional therapies, including the use of vasodilators, mortality for HF patients remains unacceptably high. The use of beta-blocker therapy for patients with HF, although seemingly paradoxical, has increasing experimental and clinical rationale.

In patients with ischemic heart disease (usually with previous myocardial infarction), patients with a history of mild or moderate HF which is clinically compensated usually tolerate beta-blocker therapy and show a mortality benefit which, in absolute numbers, exceeds that seen in groups of patients without HF. The functional consequences of beta-blocker therapy in these patients requires further study. It would seem appropriate to avoid beta-blocker therapy in those who have clinical or radiologic features of untreated pulmonary congestion and low output syndrome. In compensated patients, a small excess risk of HF can be expected.

In patients with HF associated with DCM, beta-blockade appears very promising but should currently be viewed as investigational. Current information as presented suggests that beta-blocker therapy, despite its unconventional nature, may be associated with a beneficial response in subgroups of patients with idiopathic DCM, leading to improvement in cardiac symptoms and indices of cardiac function and perhaps even life expectancy (39). Important ongoing basic and clinical studies, such as MIDIC, should better define the role of

beta-blockers in DCM. If the outcome of these studies is also favorable, beta-blocker therapy may assume an accepted role in the treatment of this interesting and important cause of HF.

REFERENCES

1. Smith SM. Epidemiology of congestive heart failure. Am J Cardiol 1985;55:3A.
2. Franciosa JA, Wilen M, Zieschi S, Cohn JN. Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1983;57:831.
3. Fuster V, Gersh BJ, Biuliani ER, et al. The natural history of idiopathic dilated cardiomyopathy. Am J Cardiol 1981;47:525.
4. Furberg CD, Yusuf D, Thom TJ. Potential for altering the natural history of congestive heart failure: need for large clinical trials. Am J Cardiol 1985;55:45A.
5. Norwegian Multicenter Study Group. Timolol-induced reduction in mortality and reinfarction in patients surviving acute myocardial infarction. N Engl J Med 1981;304:801.
6. Beta-Blocker Heart Attack Study Group. The beta-blocker heart attack trial. JAMA 1981;246:2073.
7. Hjalmarson A, Elmfeldt D, Herlitz J, et al. Effect on mortality of metoprolol in acute myocardial infarction. Lancet 1981; 2:82.
8. Hansteen V, Moinichen E, Lorentsen E, et al. One year's treatment with propranolol after myocardial infarction: preliminary report of Norwegian multicentre trial. Br Med J 1982;284:155.
9. Pedersen TR. The Norwegian multicenter study of timolol after myocardial infarction. Circulation 1983;67:I-49.
10. Rodda BI. The timolol myocardial infarction study: an evaluation of selected variables. Circulation 1983;67:I-53.
11. Beta-Blocker Heart Attack Study Group. A randomized trial of propranolol in patients with acute myocardial infarction: mortality results. JAMA 1982;247:1701.
12. Furberg CD, Byington RP. What do the subgroup analyses reveal about differential exposure to beta-blocker therapy? Circulation 1983;67:I-98.

13. Goldstein S. Propranolol therapy in patients with acute myocardial infarction: the beta-blocker heart attack trial. Circulation 1983;67:I-53.
14. Furberg CD, Hawkins CM, Lichstein E. Effect of propranolol in postinfarction patients with mechanical or electrical complications. Circulation 1984;69:761.
15. Chadda K, Goldstein S, Byington S, et al. The effect of propranolol therapy following acute myocardial infarction in patients with congestive heart failure. Circulation 1986;73:503.
16. Hansteen V. Beta blockade after myocardial infarction: the Norwegian Propranolol Study in high-risk patients. Circulation 1983;67(part 2):I-53.
17. Waagstein F, Hjalmarson A, Varnauskas E, et al. Effect of chronic beta-adrenergic receptor blockade in congestive cardiomyopathy. Br Heart J 1975;37:1022.
18. Swedberg K, Hjalmarson A, Waagstein F, Wallentin L. Beneficial effects of long-term beta blockade in congestive cardiomyopathy. Br Heart J 1980;44:117.
19. Swedberg K, Waagstein F, Hjalmarson A, et al. Adverse effects of beta-blockade withdrawal in patients with congestive cardiomyopathy. Br Heart J 1980;44:134.
20. Waagstein F, Hjalmarson A, Swedberg K, et al. Beta blockers in dilated cardiomyopathies: they work. Eur Heart J 1983;4(suppl A):173.
21. Swedberg K, Waagstein F, Hjalmarson A, et al. Prolongation of survival in congestive cardiomypathy by beta-receptor blockade. Lancet 1979;1:1374.
22. Ikram H, Fitzpatrick D. Double-blind trial of chronic oral beta blockade in congestive cardiomyopathy. Lancet 1981;2:490.
23. Currie PJ, Kelly MJ, McKenzie A, et al. Oral beta-adrenergic blockade with metoprolol in chronic severe dilated cardiomyopathy. J Am Coll Cardiol 1984;3:203.
24. Weber KT, Likoff MJ, McCarthy D. Low-dose beta blockade in the treatment of chronic cardiac failure. Am Heart J 1982;104:877.
25. Anderson JL, Lutz JR, Gilbert EM, et al. A randomized trial of low-dose beta-blockade therapy for idiopathic dilated cardiomyopathy. Am J Cardiol 1985;55:471.

26. Engelmeier RS, O'Connell JB, Walsh R, et al. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomypathy: a double-blind, randomized, placebo-controlled trial. Circulation 1985;72:536.

26b. Engelmeier R, O'Connell J, Rad N, et al. Metoprolol in dilated cardiomyopathy: long-term follow-up. Circulation 1986;74:II-309.

27. Fowler MB, Bristow MR, Laser JA, et al. Beta-blocker therapy in severe heart failure: improvement related to beta-1-adrenergic receptor up regulation? Circulation 1984;70:II-112.

28. Bristow MR. The adrenergic nervous system in heart failure. N Engl J Med 1984;31:850.

29. Francis GP, Goldsmith SR, Levine TB, et al. The neurohumoral axis in congestive heart failure. Ann Intern Med 1984;101:370.

30. Cohn JN, Levine TB, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984;311:819.

31. Shanes J, Kasabali B, Blend M. Beta-adrenergic blockade in heart failure: potential mechanisms of action. Heart Failure 1986;2:138.

32. Cryer PE. Physiology and pathophysiology of the human sympathoadrenal neuroendocrine system. N Engl J Med 1980;303:436.

33. Kline I. Myocardial alterations associated with pheochromocytomas. Am J Pathol 1961;38:539.

34. Opie LH. Effects of catecholamines on normal myocardium: implications for the failing heart. Heart Failure 1986;2:104.

35. Bristow M, Ginsburg R, Minobe W, et al. Decreased catecholamine sensitivity and beta-adrenergic receptor density in failing human hearts. N Engl J Med 1982;307:205.

36. Ginsburg R, Bristow MR, Billingham ME, et al. Study of the normal and failing isolated human heart: decreased response of failing heart to isoproterenol. Am Heart J 1983;106:535.

37. Chidsey CA, Braunwald E, Morrow AG, et al. Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure. Am J Med 1965;39:442.

38. Covell JW, Chidsey CA, Braunwald E. Reduction of the cardiac response to postganglionic sympathetic nerve stimulation in experimental heart failure. Circ Res 1966;19:51.
39. Alderman J, Grossman W. Are beta-adrenergic-blocking drugs useful in the treatment of dilated cardiomyopathy? Circulation 1985;71:854.
40. Anderson JL, Rodier HE, Green LS. Comparative effects of beta-adrenergic blocking drugs on experimental ventricular fibrillation threshold. Am J Cardiol 1983;51:1196.
41. Anastasiou-Nana M, Nanas J, Menlove RL, et al. Experimental antifibrillatory effects of calcium channel blockade with diltiazem: comparison with beta blockade and nitroglycerin. J Cardiovasc Pharmacol 1984;6:780.
42. Schwartz PJ, Vanoli E, Zaza A, et al. The effect of antiarrhythmic drugs on life-threatening arrhythmias induced by interaction between acute myocardial ischemia and sympathetic hyperactivity. Am Heart J 1985;109:937.
43. Patterson E, Holland K, Eller BT, et al. Ventricular fibrillation resulting from ischemia at a site remote from previous myocardial infarction: a conscious canine model of sudden coronary death. Am J Cardiol 1982;50:1414.
44. Patterson E, Lucchesi BR. Antifibrillatory actions of d,l-nadolol in a conscious canine model of sudden coronary death. J Cardiovasc Pharmacol 1983;5:737.
45. Goldstein S, Landis JR, Leighton R, et al. Characteristics of the resuscitated out-of-hospital cardiac arrest victim with coronary heart disease. Circulation 1981;64:977.
46. Goldstein S, Landis JR, Leighton R, et al. Predictive survival models for resuscitated victims of out-of-hospital cardiac arrest with coronary heart disease. Circulation 1985;71:873.
47. Holmes DR, Davis KBV, Mock MB, and Participants in the Coronary Artery Surgery Study. The effect of medical and surgical treatment on subsequent sudden cardiac death in patients with coronary artery disease: a report from the Coronary Artery Surgery Study. Circulation 1986;73:1254.
48. Furberg CD. Effect of antiarrhythmic drugs on mortality after myocardial infarction. Am J Cardiol 1983;52:32C.

49. Impact Research Group. International mexiletine and placebo antiarrhythmic coronary trial. I. Report on arrhythmias and other findings. J Am Coll Cardiol 1984;4:1148.

DISCUSSION - 4

Dr. Morganroth: Dr. Cohn, do you accept the concept that the amrinone-like drugs really should be looked at as vasodilators that don't cause as much hypotension as the ACE inhibitors? Is this an important classification issue.

Dr. Cohn: As you know, the separation of inotropic and vasodilator effects of drugs is extremely difficult in drugs that have both actions and I have not tended to classify these drugs as vasodilators but as inotropic drugs with vasodilator effects. It may be that the vasodilator action is playing an important role in the hemodynamic effect. If there is clinical efficacy, I don't see how it is going to be simple to separate whether the clinical efficacy demonstrable is related to its vasodilator effect or to the inotropic effect and this is an age old problem. In the whole animal or whole human being, to try to extract a total hemodynamic effect, what if that effect is related to cardiac stimulation directly? What is related to cardiac stimulation reflexly and what is related to the vasodilator effect in the periphery? You could add that as another group of vasodilators, PDE inhibitors but I still would just as soon classify those drugs as inotropic.

Dr. Morganroth: To me there is a conceptual concern. For example, if IRB's accept the hydralazine and isosorbide data then one would not want to randomize high risk severe heart failure patients without allowing those drugs to be part of their routine regimen and therefore with these vasodilators in the background, how would you test an inotrope that also had vasodilator properties? Can vasodilators of different mechanisms be added together?

Dr. Cohn: They probably can be. We don't know what the additive effects of drugs like hydralazine and nitrates are with PDE inhibitors. There is certainly evidence to suggest that an ACE inhibitor can be added to another direct acting vasodilator and get an additive effect. We don't test classes of compounds, we test drugs. If you have someone on hydralazine and isosorbide and then you add enoximone to them, you are testing whether enoximone added to the dilator produces a beneficial effect. Whether it is producing it by additive effect on vasodilation or by inotropism doesn't concern the FDA and probably shouldn't concern us. If the drug is effective, it is effective.

Dr. Somberg: Why do you choose nitrates and hydralazine? Do you think the effect would be as good if you used nitrates alone? The second corollary to that is, what agents given that explanation of the vascular effects of the different drugs, are now being used generally or being developed that might have that same useful result that ISDN and hydralazine had? Would Captopril or Enalapril have that same outcome if the VA did another multicenter study?

Dr. Cohn: Obviously the reason we chose hydralazine and nitrate together is because their effects were complementary; that is one worked on the arterial side and the other worked on the venous side and when we studied those drugs acutely years ago, they produced a dramatic hemodynamic effect that was favorable. That is the wedge pressure came down and the output went up and it looked just like intravenous nitropresside which is the standard vasodilator that was introduced to deal with acute pump failure. The pharmacologic

mechanism of those drugs is what led us to choose them in combination. Can one tease out whether the response in VHEFT is related to one or the other or the combination? Obviously not. We didn't study either one alone, we studied the two together and we knew when we embarked on that trial that if the therapy was effective, we wouldn't know whether it was one drug or the other, but the fact that the two drugs together are quite well tolerated, have long been in use in medicine and have no long term toxicity to (at least in this study there wasn't). There is really little long term toxicity that we knew of that you have to use both even though it is possible that either one or the other was effective. As you know hydralazine in other trials has not by itself turned out to be very effective, but there hasn't been a mortality study done and that is what we have reported here. Nitrate in other trials has been more effective on exercise tolerance, quality of life, and symptoms than in mono-therapy but once again there have been no mortality trials. We have the two together and they reduced mortality and I would say it has to be viewed as a response to the combination therapy. Are there other drugs that have similar effects? Yes. Any drug that has venodilator or capacitance effects and arterial effects will produce a similar hemodynamic response particularly if it doesn't have a simultaneous cardiac depressing effect. One can see this with the converting enzyme inhibitors which produce a similar effect; A little less effect on the arterial side so you don't get quite as much rise in cardiac output and you get a little more fall in blood pressure. I don't think we understand why that is. That doesn't follow from our known circulatory effects of those drugs. The blood pressure falls a little more with Captopril and Enalapril and the output doesn't go up quite as much acutely, but otherwise the pattern of effect is quite similar. The calcium antagonists have a little less venous effect, but they do lower the wedge pressure and raise the cardiac output but some of them have some negative direct inotropic effect which may worry people a bit, and there are some other vasodilators out there that seem to have both venous and arterial effects which could play a role in therapy and might be a replacement for hydralazine and nitrate.

Dr. Temple: The results of this trial as intervention trials go are extremely impressive. They are more impressive than other trials that have shaped national therapy on a number of areas for example is a purer result than you would say the VA studies in hypertension, where there was a mixed end point and so on. Certainly more impressive than the results of the recent trial on lipid lowering which used one tail tests and had an end point that was complicated. Can you speculate on why we are talking about phophodiesterase inhibitors here when there seems to be something that changes mortality in a group of people who are fairly sick. What is you explanation why there doesn't seem to be overwhelming enthusiasm and the explanation could be scientific or economic?

Dr. Cohn: I don't know what the degree of enthusiasm is. I do think the second part of your question, why are we looking for other drugs. We haven't solved the problem. People are still dying. I didn't point out the survival after 3 years, in the small number of patients who were followed into the 4th year, the difference in

mortality became very small. Is that just a function of sample size or does that really mean that we have just shifted the mortality curve to the right but eventually you are going to die. The curves will all come down to zero eventually, it is just a question of when. We are not interfering with the underlying disease process. Nobody could convince me that these vasodilators are changing the underlying myocardial disease. If there is a contractile abnormality in the heart, I would like to deal with that directly, as a more effective way to reverse the disease early. We are dealing with it through the back door. We take a depressed heart and improve its ability to empty and hopefully change progression of that heart failure because by letting it empty better and reducing wall stress and maybe inhibiting the development of more hypertrophy and maybe in the long run the ventricle and the myocardium are benefited by that but we are not interfering directly with the abnormality, which is a contractile abnormality of heart muscle. If we could develop a drug which would directly influence contractile protein and make it function better and not harm it, and thus reverse the process that way, we might not need the vasodilators and it might be a more effective way to treat it. I am all for developing other drugs. We have not solved the problem, we have palliated.

Dr. Sonnenblick: I wouldn't disagree with what you are saying Jay and that is that these patients are still dying on nitroglycerin and hydralazine which we have used for a number of years and we are happy to see that there is a reason we should be using them. There is a problem in how one states numbers. If one wanted the CASS data to look good, instead of saying that the mortality went from 6% to 5%, you would say that the survivability went up 20%. Rahamatoola has emphasized that in a very nice editorial. In BEHAT, you had 20-30% improvement by lowering something from 6% to 4%. There is only a 20% mortality in this group, and this is about half of what the overall group as you would agree, when the ejection fraction gets down into the 20's. These are patients with mild heart failure with an ejection fraction of 30, especially with that wide standard deviation and these patients generally do pretty well, although the mortality figures that you start out with are about half of what generally is seen and there is a benefit in the curve being moved a little to the right and the mechanisms that you have mentioned are fine. That is hardly a solution to the problem that the mortality figure went from 22% to 16% and then started to approach again after the third year. It is a benefit palliative in the short term. One has to distinguish that from the beta blocker effect where the curves seem to flatten off perhaps in certain studies, that you may be getting a mechanism underlying it. The other thing is these patients with just nitroglycerin and hydralazine are dying in pulmonary edema when they get very sick and they require further therapeutic input. That is why one keeps developing the drugs, not merely to have another drug on the list. There is a therapeutic need. These patients are very sick and we see them in the hospital. You are describing the chronic mild heart failure outside complicated by a lot of diastolic dysfunction which responds very well and may not even need inotropic agents, so there is a phasing

process, small gains, but hardly a reason to state one has accomplished an end point.

Dr. Cohn: The only disagreement I have with you is the suggestion that this is not the kind of population that we should be studying. This is the population. The higher mortality figures that you and I quote from our own referral population in a university hospital setting has a 40-50% 1 year mortality and that is a very small subset of the large mass of patients who have heart failure out there. Most of them have milder failure and are being treated now by their physicians with diuretic and digitalis and sent home. I think that is the group we have to have some impact on to prevent them from reaching the point that we see them in our university setting. Our attempt in this trial was to go out and get a non-referred population, albeit a hospital base population but screening for LV dysfunction and not taking the patients who are sent to a special care situation because they failed all therapy and they are not class 4. We know that is a depressing group to treat other than with transplant. The beneficial effects of drug therapy pale in comparison with transplant. We have now done 97 heart transplants and 50-60 of them in the past year, and we haven't lost a patient in about a year and a half. They are leaving the hospital an average of 7 days after transplant and going back to work. This is a totally different kind of therapy. We are making small inroads, but not making the impact you would by putting in a new heart.

Dr. Sonnenblick: That is exactly why I was trying to say that you have to decide which group you are working on and that is what Dr. LeJemtel was trying to point out. The therapeutic input is quite different at different points in the disease and this is one segment of that disease population.

Dr. Temple: I don't think that answers my question. In the terms you wanted, namely salvaged bodies per year, or in the percent reduction, this is an impressive result as any intervention study I can think of.

Dr. Sonnenblick: Dr. Cohn didn't say there was a symptomatic improvement in these patients and I hear there is very little symptomatic improvement if any.

Dr. Temple: That is a different question. I am just talking about bodies saved. This is more impressive that what you get per year from hypertension, it is more impressive than what you get from beta blocker post infarction treatment, it is more impressive than what you get from aspirin treatment. It is more impressive in bodies saved per year than anything I can think of. That doesn't mean you should stop looking for other drugs to treat symptoms, but for this population of people, that is the people that Dr. LeJemtel didn't say need the inotropes, that is people who are going out, there seems some disproportion between how impressive that result is and what everybody is saying. I don't think I have heard the full explanation. Or is it that you don't think symptomatic improvement is so great with this treatment.

Dr. Sonnenblick: I think the problem is that the symptomatic improvement isn't there. One would have liked to see further benefits. The other problem is that these patients still progress on this wonderful form of therapy and do get in continued trouble.

It is simple to give them this as a start, but I am not sure where one goes from that point in time.

Dr. Temple: But people aren't saying give them this as a start and try to add something to do even better. This discussion is sort of parallel. In other words, to put it plainly, if for these class 2½ to 3 people, this seems to reduce mortality in a substantial way, why would one look at the phosphodiesterase inhibitors especially if you really believe they are vasodilators and therefore work the same way in the same population in any other way than to really look at mortality effect, and see if it is as good. Isn't that the question if you believe this outcome?

Dr. Sonnenblick: It depends on which question you ask and which group at a given time and here you have a small effect on mortality and these curves do start to come together. You are also looking at curves that have a rather flat slope that is similar. They have been moved slightly to the right and you could also in that have errors of which patients entered that may not have had primary heart failure and there are a fair number in there. There are also a group out of the VA hospitals which are well known to have a large base of alcoholism. They are not necessarily the grandmother with heart failure, maybe but not necessarily. I think there is a lot of selectivity when you study patients in the VA setting in a chronic failure state.

Dr. Temple: So one has to replicate that finding outside.

Dr. Sonnenblick: Perhaps. I think that is where the ACE inhibitors may have a better role perhaps and still need to be studied in that regard. It is attractive to think about normalization of electrolytes at the same time one inhabits the renin-angiotensin system. I wouldn't throw that out as a major way of perhaps impacting in the same fashion and over a longer period of time. The same thing with the beta blockers.

Dr. Temple: What I still can't figure out is if one has doubts about the generalized ability of the finding to a non-VA population, is it more logical to take the same therapy and study it in another population or a completely different therapy that has never been shown to reduce mortality in anybody. Which makes more inherent sense?

Dr. Sonnenblick: We do use the nitrates. I don't even see it as a question in study anymore. I see it as a baseline therapy we use very regularly. I think the next step is what do you do to get beyond this.

Dr. Cohn: I think the problem is that if you looked at the data we were shown yesterday about how physicians are treating heart failure, relatively few of them are using nitrates and certainly fewer using hydralazine to treat heart failure, although you may use it. It is apparent that the general practicing physician in the community has not been given the message. One of the reasons that he doesn't have the message is that no one is pushing it. It is not approved for that use and there is no pharmaceutical company interest in selling this cheap drug out there that is generic and that does impact upon drug usage in the community.

Dr. Sonnenblick: I think it is not so easy to have very large doses of nitrates aboard with big doses of hydralazine. There is a tolerance problem that we have seen on occasion.

Dr. Yusuf: Dr. Temple kept saying that there is a tremendously impressive result with VHEFT and , why don't people use it. If that result is what it seems, yes it is a tremendously important result, ten deaths prevented for every 100 people treated. That is better than anything we have in secondary prevention, but the question is is that figure reliable? We know of many areas where the first trial or one trial has come out with tremendously positive results. Take intracoronary streptokinase for the instance. The study from Seattle: 400 patients 80% reduction of mortality at 7 days and it narrows down at one year, it is no longer significant. Eight other trials you don't see anything. The 9th trial from Holland, nothing at 7 days, but at one year, there is statistical significance, so you can focus on what you want depending on your own biases and maybe it is true that maybe the drug does work early and later on it goes away. We really need replication of that. I can think of all areas, like the slide that Jeff Anderson put up on Timolol, Metoprolol and Propranolol, one trial showing a 45% effect, another one 25% effect. You put all the trials together other than dose, again it is a much more modest effect. I think that 35% probably is an overestimate. What we really need to do is to be sure whether that is true or not. The other way of putting this trial in context, is if you just take one death out of the trial and it crosses lines, the study is wholly nonsignificant and in fact if the analysis is done, the standard way that we want to do most analyses of most trials is that if you look at results many times, and if you have multiple drug groups, then the results are not significant. I don't think one should focus on that 35% alone. The trial is a substantial achievement and we shouldn't take anything away from the trial because it doesn't answer all the questions that we want. But at the same time, we shouldn't oversell the trial. I think it is a very impressive result that certainly needs replication. It is a borderline result and that is the way the New England Journal of Medicine paper was written. It was a very balanced article. Today we shouldn't say we definitely have evidence that it changes mortality. We just don't. It is the right trend, but it is not totally convincing.

Dr. Morganroth: It is an impressive border line result.

Dr. Temple: Dr. Yusuf, I still would put my question to you. If you had no other result showing mortality effect of all the possible therapies available, which would you choose to do another study in based on available information assuming everything you say is so.

Dr. Yusuf: There are two things. I would decide for myself whether it was a class effect or not and here I use judgment. Judgment based on what I know of mechanism and method of action and I think most of us believe this is probably a vasodilator effect. Some are more effective than others and most of us believe who are in the field that as a vasodilator perhaps the ACE inhibitors are more effective and I think that has even persuaded the people who have done the VEHEFT study because the VHEFT to study is precisely that, comparing an ACE inhibitor versus ISDN. Those of us who are doing SOLVD believe that the vasodilators have a pretty good shot at improving mortality and the VHEFT results have strengthened our belief in that, but we think maybe ACE inhibitors are a better class of agents. Suddenly they are a better class of agents as far as

compliance is concerned and side effects are concerned. We are not totally disregarding those results, but we are using them in the context of not just the numbers from VHEFT but what else we know about the mechanism of action of these drugs so there is nothing inconsistent.

Dr. Lipicky: I was going to say the same thing. I am not sure that that trial is the basis for decision making at this point in time. Secondly, that the choice of agents seems rather difficult because I am not convinced from the data that Dr. Cohn showed or other data I have seen that in fact ISDN does have a chronic hemodynamic effect and therefore I am not sure on the results of that trial that one should use the combination of hydralazine and ISDN. If one did in fact want to make that single trial the basis for the decision making and it seems to me that there is a lot more to learn about that effect and if the effect is able to be replicated, how it occurred, prior to beginning to make decisions that say that some real fact has been established.

Dr. Temple: I am still struck by the contrast between the total acceptance between the VA studies in hypertension which you could argue about it a bit, but probably never been replicated, maybe HDFP replicated, you could say that, but it happened 20 years later, by the enthusiastic support of the lipid research trial which is no where in comparison. It used a much more complicated and difficult endpoint. I think it is interesting to think of these things as class effect, but it isn't totally class effect. That is quite a big leap.

Dr. Lipicky: There are two possible explanations. One is that people make decisions on the basis of their biases or secondly that in fact people have learned on the basis of those kinds of efforts in the past that you really do need to be replicated and that one shouldn't jump on the bandwagon right off the bat.

Dr. Temple: But is it replicated?

Dr. Lipicky: It is in fact. There is a large ACE inhibitor trial.

Dr. Temple: If that doesn't work out, what would you conclude, that isosorbide and hydralazine don't work either? That wouldn't be reasonable.

Dr. Lipicky: Different problem. Is the question you are asking why is not someone doing the trial that is a placebo vs hydralazine, and ISDN combination?

Dr. Temple: One would think from everything you said that it would be perceived as a matter in heart failure at least of pretty high urgency to either decide to accept the single trial which obviously would give people trouble because it is only one, and get out and replicate it.

Dr. Lipicky: I wouldn't try to replicate the trial in itself. I am not being critical of the design or the decisions that led to the trial and I don't mean to imply that I am, but if one were going to pursue that particular avenue with those two particular agents, then I wouldn't simply replicate the trial, I would try to figure out whether it was ISDN and/or it was hydralazine and/or the combination. It seems equally plausible to rather than simply replicate that particular trial to test the hypothesis that it is indeed some kind of a generic thing and take another vasodilator and see if in fact the other vasodilator performs in the same fashion.

That seems as sensible as simply replicating that particular result and so I think the whole thing can be explored in more than one way.
Dr. Temple: Nobody is setting out to see if the crucial finding is replicable and studying another vasodilator alone doesn't do that. The three-way study you are describing would. That would make excellent sense and would add further evidence to the question of whether there is class effect. That trial doesn't seem to be high on anybody's agenda.
Dr. Cohn: I don't think that one can stand back and be rigid about this thing and insist on replication and I would be the first to say that one trial does not indeed prove truth if that is what we are after here. This was a small study by traditional multicenter studies. We had only 642 patients and compared to the lipid study, the VHEFT trial is a very small population. The borderline significance, if that is what it is called in this study, is related to the size of the study, not to the magnitude of the effect and it is important to keep that in mind. When you have a borderline .05 result with a two-tailed test in 5000 patients, you are clearly dealing with a different situation than when you have a .05 p value in 600 patients. Now that statistically may mean the same thing, but in terms of the impact and the potential of the therapy, I think it makes a considerable difference. Yes it is nice to replicate and unfortunately it is probably not going to be done. We are not going to repeat the trial. It is our thesis that it is unethical to have a patient on a long term placebo controlled trial where they are not given a vasodilator regimen and that has to be our position because that is our result and our interpretation of the results is that we save lives, and I would not knowingly expose a patient to a long term trial on a placebo along with dig and diuretic to find out if a vasodilator regimen worked. Our position is that the issue is resolved enough to influence the planning of subsequent trials. Now you have a therapy that hemodynamically is effective, improves cardiac output, lowers wedge pressure, does all the things that we want it to do and that was the reason we employed the trial. And now we put it into people and we find that it prolongs life. It seems to me that that is enough to approve this therapy even if it doesn't prolong life, it certainly did not harm life expectancy and hemodynamically it had a favorable effect, so for me to say we have to stand back and not let people use this therapy until we prove again that it prolongs life is not reasonable. How many drugs do we have out there that have been proved to prolong life? Not very many and yet they are approved for management of a syndrome. We have a Timolol study that was done and that single multicenter Timolol trial led to approval of Timolol for secondary prevention of myocardial infarction. It wasn't replicated right away. It was approved before replication. There is precedent for using one multicenter trial to make judgments.
Dr. Temple: It has been true that one trial is sufficient policy wise to become accepted for labeling. That was certainly the case in Timolol. We sort of knew BEHAT was coming and that made me feel a little warmer about the concept but we approved it before we had those data or had access to them because we didn't think anybody would be willing to randomize people in those categories to placebo or beta blocker anymore. The p values for the Timolol trial are

very low. I think .001 was about what it was and the strength of the observation was more forceful and that helped us make that decision. There have been instances in which a single persuasive trial led to labeling. I should mention that labeling for antihypertensive agents does not say that they improve life expectancy or decrease strokes. They are all just for lowering blood pressure at the present time at least in part since no one has asked for anything else. I don't know about reserpine and diuretics.

Dr. Lipicky: That is part of the problem here. The most eloquent part of the pitch Dr. Cohn is an ethical and moral pitch. In fact from a science vantage point one has an answer that is explicit and I have trouble reacting to ethical moral pitches and have a lot more comfort reacting to data to established things. It isn't clear to me what one would be approving what one we haven't been asked to. Secondly, there is no combination drug that contains hydralazine and ISDN.

Dr. Temple: Yes there is. You could be asked to approve by the manufacturers of Isorbide a claim that says used in conjunction with hydralazine that the drug does this and you could be asked by the manufacturers of hydralozine to approve labeling or either of both to approve labeling that says used in conjunction with Isosorbide.

Dr. Lipicky: Yes but we haven't been.

Dr. Temple: Ray raised another complication and that is what do you do when somebody has done the study that perhaps isn't the one you most prefer, namely they haven't done a factorial study in which they compare each single therapy and the combination with placebo but the result is a substantial reduction in mortality. Again, although it hasn't come up regulatorily, there is no trial showing that a single agent prolongs survival in hypertension. All of those trials used a variety of combinations to achieve a certain blood pressure lowering and I remind everybody again what most of the data consists of is data on thiazides and reserpine, two drugs with particular properties that are not shared by all drugs. Reserpine is very long acting, it lowers the heart rate, it does a lot of things. Not all drugs do that. You encounter this in the oncology field frequently where someone has studied 8 drugs at once, that is the worse case, but often 3 or 4 and gotten a dramatic effect but has not necessarily built up the regimen with complete rationality going from one drug to two, to three to four drugs. The question is what do you do if a survival improvement has been shown and we grappled with this some time ago and took the position I believe we have an internal memo to the oncology group. Dr. Finkel wrote sometime back that there are cases in which we would ignore the difficult problem of which drug was contributing when there was a clear change in mortality because we didn't think that anybody would want to be part of the trial to discover which of the components led to increased mortality. I usually try to think what would I do on my child as my moral litmus test and I wouldn't want to find that out unless the toxicity was unacceptable or some very urgent reason arose to make you find out. We were going to face that problem in full with Paris-II. If a dramatic effect was seen and we couldn't decide that aspirin alone did it, what were we going to do about aspirin plus dipyridemol if there was a dramatic reduction in mortality. We

solved that for our satisfaction by approving aspirin. Now we don't have to worry about that. There is a point at which it would be very difficult if the study was overwhelmingly persuasive and everyone believed it, to say I want to know if it is the hydralazine or the isosorbide and I am going to use people to find that out, I think that would be questionable.

Dr. Lipicky: I am sure it could be, but there are more issues than that with the trial it seems to me, and although one could value life above all else if in fact one doesn't know that people felt better during the time that they were alive or were able to perform better during the time that they were alive, it seems that one would want to weight that prior to making some kind of decision and indeed what is it that one is considering. Basically from an antihypertensive drug vantage point in which what one is talking about the treatment of hypertension, and lowering blood pressure, not saving lives or aborting strokes. The indication as it is written for hypertension is not to prevent strokes or increase lifespan. It is to lower the blood pressure.

Dr. Temple: True, but the only reason anyone is doing that is for the reason that you named.

Dr. Lipicky: I hear that, but in the circumstance of congestive heart failure, one would be now saying that the treatment of congestive heart failure the indication was to prolong life, not to treat congestive heart failure, because on the basis of the trial results at hand, one wouldn't be able to make that recommendation.

Dr. Temple: I agree completely, but take post-infarction.

Dr. Lipicky: That seems a little strange to me.

Dr. Temple: That is normal policy. Take the post-infarction setting. What are you treating there. You don't make people feel better by putting them on propranolol unless they have angina. On the whole you make them feel worse. They tend to get depressed and a variety of things that make their life less good than it was.

Dr. Lipicky: I am not sure that was wise. I question that. Why is that an indication.

Dr. Temple: Because some people would like to live longer. That is a reasonable thing to do with a drug. Physicians do in fact weigh who they put on beta blockers. If people are in the low risk category, they tend not to treat them.

Dr. Lipicky: Why does it have to be an FDA declaration that it is indicated to save lives? Why is that something that must appear in a package insert as an indication? It seems to me that what should be in the package insert is that this drug is useful in the therapy of some disease, and indeed that the medical community know what purpose they are putting it to. We do not currently require mortality as an endpoint for approval for a claim for congestive heart failure.

Dr. Temple: Just because we don't require it, doesn't mean that it is not a legitimate claim. Our rules are that you have to prove what you seek to claim. That the sum and substance of the effect of this requirement in law. You have to do what you say you do, and there is no inherent rule for saying you cannot have a claim that you reduce mortality in people with congestive heart failure. There are several possible claims that one could make and they are all perfectly reasonable. Reducing mortality is reasonable and one

would definitely want to characterize miseries that taking that therapy induces because that is part of the decision to use it. You could also say that you improve symptoms. Anyone of them is O.K. and all are legitimate and they all strike me as reasonable. As long as nobody asks us to approve it, we won't say a word and the community can decide by itself.

Dr. Cohn: The end point of the trial was mortality and that is why we have emphasized that in all of these discussions and in our publication. We have lots of other data that will be coming out soon and in fact the exercise data will probably be presented at the American College of Cardiology meeting so we will be able to provide more support for the ancillary symptoms and signs that occured. Ejection fraction did significantly go up from the ISDN and hydralazine group and not in the other groups which again lend support that there was some active pharmacologic effect going on there and it wasn't just a happenstance. The more data that go in the same direction, you are a little more persuaded than if it is one observation.

Dr. Yusuf: We don't argue what the trial numbers are or the p value or anything but what we are talking about is, is it persuasive enough to say it is unethical not to use it. That really is the issue. I think we are continuing to make the classical mistake that has been made all along of looking at that trial in isolation. I agree with you Dr. Temple that the LRC is no stronger or weaker than this particular trial in itself.

Dr. Temple: It is obviously much weaker. It uses a different end point, a less reliable end point and a one-tail test. It is obviously statistically weaker.

Dr. Yusuf: Let's say what you say is right for the moment, but the reason to accept the LRC and the hypothesis that cholesterol lowering is going to be good. There are 30,000 people in other trials other than the LRC in which you have clear reduction of nonfatal MI and cardiac mortality so that if one were to just have LRC, I would agree with you, I wouldn't be persuaded. I agree that the hoopla around LRC may be distasteful to many of us, but on the other hand, you really have to look at it in the total context of what the totality of the evidence is and not just that one trial. We have no epidemiology of vasodilators: we have no animal experiments, on hydralazine or ISDN by improving survival. All we have is this one trial. It may be true. I personally believe it is a class action, it probably is true. The question of ethics goes both ways. If it was really that persuasive to everybody, that it must be used in everybody, I would like to ask the question why is it we have to design it the way it is. Shouldn't everybody have got this combination.

Dr. Cohn: No, we have demonstrated in this trial that the placebo group is no longer acceptable. We have not eliminated the possibility that in other regimen of similar action might even be better and there is obviously lots of data out there to suggest if anything the ACE inhibitors might even be more effective than this regimen. I have no problem ethically in offering the patient the choice of one vasodilator regimen which has been demonstrated to prolong life and another vasodilator regimen which is approved by the FDA for the treatment of heart failure. I do not think it is

ethical to have a placebo group any longer in the long-term trial. That doesn't eliminate placebo group in short term, a few week trials of drugs to see what their hemodynamics are.

Dr. Yusuf: But as far as we know, these inhibitors don't affect mortality

Dr. Cohn: But we don't have the data yet.

Dr. Yusuf: Like any trial, ACE inhibitors after 5 years of SOLVD and BEHAT and everything else could come out negative, but here is a trial with an agent that you think works, surely why should you deny patients something that is proven to work versus something in which there is a question mark if you are that sure it works.

Dr. Temple: There is some point in that. On my ethical linear analog scale, keep treating people with placebo. You have to talk from the point of view of the VA which after all did the study and is in a more difficult position than someone external; but studying a new agent when you know one that prolongs life does raise problems, but not as severe as offering no treatment at all.

Dr. Yusuf: I think it all depends on how convinced you are that the data are clear cut and it does affect survival. I think most physicians treating patients will use not only the trial data but mechanisms. What other data are there and personal bias, and usually those things are more correct than basing it on one trial.

Dr. Maroko: I would like to ask the question, why not analyze mortality also from the point of view of cardiac mortality. I understand your point, Dr. Cohn that some bias can creep into dividing mortality into overall mortality and cardiac mortality and sometimes it is not clear. But wouldn't the point of your study be stronger if you can show besides overall mortality, specifically mortality due to heart failure as opposed to car accidents, will also increase and from a regulatory point of view maybe, it is easier to say that this drug proved to decrease mortality specifically of congestive heart failure and not only of mortality.

Dr. Morganroth: Or at least eliminating the clear cut deaths such as cancer, accidents, suicides if one can't make the distinction between a heart failure death and other types of cardiovascular deaths.

Dr. Cohn: Obviously we have done that. The number of clearly non-cardiovascular deaths are very few. Accidents even become a problem as other people have had. You don't know whether it is a cardiac death or not. In this kind of a population, there are very few non-cardiac deaths and to try to tease them out, there is a terrible problem. You have somebody with cancer who develops pneumonia and dies. It is clear that the heart disease has played a role in the death occurring at the moment in time. It is very hard to be absolutely sure. That is why I think the purist thing is that we can definitely count bodies. I am skeptical that when total mortality doesn't work out and you sort of go back over it and say, let's just look at the cardiac ones. You end up with softer data, so once you have the overall mortality it is very fair to try to separate it out, but if they don't have an effect on overall mortality, I think you are in a little trouble.

Dr. Packer: First a question to Dr. Anderson. All of the trials that you have shown with beta blockers have excluded prior to randomization, patients who were intolerant of beta blockade.

Obviously you are using small doses. It is curious. If you think of catecholamines or neurohormones in general as playing both a beneficial and detrimental role. Those people who have the highest levels of catecholamines are most likely to deteriorate during initiation of therapy but are also probably from a conceptual point of view more likely to benefit during long-term treatment. Those patients who are intolerant of beta blockade presumably have very high event rates and therefore you are reducing the number of events and I am curious whether that strategy may be reducing your chances of finding a significant finding in a double blind placebo controlled trial. Obviously it is a very practical solution. I am just wondering what your thoughts are.

Dr. Anderson: I agree with that. That is why we analyzed our own survival data both by intention to treat which I think is the cleanest way to do it for that reason as well as actual treatment approach. One problem is numbers. It is hard to get that many patients into a trial and it improves your power if you can focus in on patients that are actually going to get the drug versus not get that. I think in my own mind an equally good hypothesis would be that the beta blocker therapy in fact as you say are sicker and are going to die anyway and once they get switched over to placebo, that is going to make it look better and it may be just a matter of selection bias rather than a matter of treatment effect. On the other hand, as you say, they may be the ones that if you can get them on therapy, they may do the best and that might be a problem in terms of how we approached therapy, we didn't start with a low enough dose. We were impatient enough, and I can tell you that is a real variable. As a matter of fact, the longer we have used beta blockers, the more success we have had getting a high percentage on them. I would guess 80-90% can get on the drug. Perhaps the others ought to have transplantation or inotropes or something else. Obviously it would be nice if we could get enough numbers that we wouldn't have to worry about the crossovers. I would just like to add that the particular trial design of testing a drug first and then going on further into therapy after an initial trial is being considered for the cardiac arrhythmia suppression trial rather than for similar reasons. This is a much bigger trial.

Dr. Packer: The situation actually is somewhat analgous to the converting enzyme inhibitor analogy in that the patient is likely to become hypotensive during initiation of therapy are those with the greatest activation of the angiotensin system who presumably if you think that angiotensin II is bad for people in terms of mortality are the ones most likely to benefit if you could keep them on the converting enzyme inhibitor and most of the time you can. The hypotension is an early phenomenon disipates and the heart failure sometime with the beta blockade and particularly with the BEHAT sub-analysis was an early phenomenon and it could be that the patients who are most likely to benefit and most desperately need that kind of intervention are being eliminated.

Dr. Anderson: I agree completely. Actually in my study, we are starting with 5 mg metoprolol twice a day. We haven't had any person that hasn't been able to tolerate that, but that is the test dose, if they pass that, then they get into the trial. If they don't pass that, then granting what you said, they are going to have to

have another approach. Obviously beta blockade is not a magic cure-all. It is surprising how many people you can get on. That is the thing that to me has been surprising with my initial biases being the same as others, and we keep treating sicker and sicker people with it. There seems to be no a priori way of deciding if a patient will or won't tolerate at least some beta blocker therapy by how sick they are. We have had transplant candidates go onto it, some have been able to get off the list, not everybody, but at least be able to take it in very small increasing doses. That has been the increasing observation rather than the other way around.

Dr. Packer: Jay, I appreciate your concerns about the lack of a post catheterization vasoconstrictor phenomenon and I think all of us have been trying to pursue for a long time the concept of what is a true basal state, something which is unrelated to the measurement procedures or in some ways similar to the Heisenberg principle, the more you try to get closer to it, your methodology may be progressively affecting your measurements. We do not use sedatives prior to our invasive procedures, and I know that is not used commonly in a number of other centers who have also decided to catheterize patients the day prior to performing measurements the day after for drug effect. Is there anything that you are doing that is an attempt to avoid the anxiety related vasoconstriction?

Dr. Cohn: We don't use sedatives either and I guess the patients are fairly relaxed. They are not in a formal cath lab. They are in a bed in a quiet room and we often have music. There is an informal atmosphere. I have visited other labs and I think the techniques are not that dissimilar. We don't see any systematic effect, and the only reason that I raise that issue is that out here in the audience is a large group of people who plan clinical trials and I have been concerned that many of the protocols come through these days asking for the catheter to be put in the day before. I think that adds risk, it adds cost, and I don't think it is cost effective because I think one need not see this effect but I respect your data and I think that in the series you looked at, this was apparently true. It did not occur in the people who were catheterized the second time and it may in effect mean that if you acclimate the patient to the environment and the personnel that they won't see that and all of the patients that we study have already been in the lab. They had their stress test, they know the personnel, they are comfortable in the environment and that may be the important factor.

Dr. Packer: One solution that Joseph Franciosa offers is that his concern is it doesn't matter when I put in the catheters, it doesn't matter when I feed the patient, I am going to use a concomitant placebo and do an intergroup comparison and the whole thing will wash and obviously that is an alternative solution.

Dr. Sami: The patients who have received beta blockers in the trials that you have examined so far, let's leave the BEHAT trial because they all have ischemic heart disease, but in the other groups, what proportion of patients have congestive cardiomyopathy or heart failure of other etiology and do you have any insight as to perhaps what may make beta blockers work? Is it more in patients with ischemic heart disease than to the other groups.? Do you have any thoughts about that?

Dr. Anderson: In our trial we have limited it to idiopathic dilated cardiomyopathy. We have left coronary disease, LV dysfunction, studies to the BEHAT and other studies. Incidently, I think that there isn't as much real good data for what happens functionally. I think that there are additional studies that are required in patients with ischemic heart disease and LV dysfunction in terms of function. I think we know more about what happens in mortality if you can get them on it. We have focused our studies, the Swedish study, the Chicago study, the Stanford study, were all in patients with dilated cardiomyopathy, not of alcoholic etiology. Probably post-viral in most cases, but that is still a fairly heterogeneous group of patients. I think the response may be different in different groups of patients clearly. I think it is important to emphasize that that is the group of patients that we have been looking at.

Dr. Pitt: I wonder if Dr. LeJemtel would expand his comments on the patients with compensated failure who he suggested that perhaps the converting enzyme inhibitors don't play a role at least in a portion of them. There are a few facts, first I wasn't really aware that the long term effects of the converting enzyme inhibitors depend upon the activation on the renin angiotensin system and secondly if you look during exercise, even though resting values are normal, the renin angiotensin system is activated, more so in failure than in normal so it is possible if you were going to look at some exercise parameter that the converting enzyme inhibitors may play a role in compensated failure.

Dr. LeJemtal: You have seen our manuscript. You know during stress you can have increase in renin angiotensin activity, but nobody is studying that really. We don't know how long after exercise and if it works out it is probably because during exercise you have reducing renal blood flow on a patient with compensated heart failure. The duration of the decrease in renal blood flow can be more prolonged in a patient with heart failure than in normals. It is a point but nobody has data on it. I did not mention because I was trying to speed up my presentation.

Dr. Cody: I don't think you can say anything about the renin angiotensin system long term in diuretic treated patients because there really isn't much that you can measure except angiotensin II or aldosterone. Very few people if any measure that. You can't go by sodium excretion because it is abnormal to begin with and, dietary sodium intake has never been carefully analyzed in any study that I have seen long-term. You can't go by the renin itself because it is a reactive increase. You can infer some things by the reactive increase, but you can't go by the renin level either. It is a problem, but very few people keep their diuretics constant despite window dressing to that effect. The other thing is, I don't think there is good convincing evidence about what the renin angiotensin system does during exercise except in patients where large doses of diuretics are administered or sodium restriction is tight. That data doesn't exist. We don't see very large reactions, large increases in renin in normals, hypertensives or heart failure during exercise.

Dr. LeJemtel: Dr. Cody, there is some data on hypertension get more increasing blood pressure during exercise and at r data is from Belgium, I think.

Dr. Cody: We have some of that data to, in about 30 pa and that is mostly systolic and mostly relates to the incre cardiac output. The increase in diastolic is very small an individuals actually goes down. It is mostly systolic and relates to the increase of cardiac output. The increase in diastolic is very small and in some individuals it actually down. There is another reason why renin can go up during e sympathetic tone stimulates renin release and clearly catec go up on exercise also.

Dr. LeJemtel: But systolic and diastolic pressure are lowe during exercise on Captopril than on placebo. More so than I don't know what it means.

V. CLINICAL TRIAL ISSUES

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WHAT CHF TRIALS HAVE SHOWN TO DATE AND WHAT IS NEEDED?

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INTRODUCTION

Improving the situation for the growing number of CHF patients is a major and growing public health issue. It has been estimated that approximately 2 million Americans suffer from CHF (1). This number is likely to increase over the next decades with the improvement of the average life expectancy since the prevalence of CHF is highly associated with increased age. Moreover, advances in the medical treatment of arterial hypertension and myocardial infarction and the surgical treatment of multivessel coronary artery disease and congenital and valvular heart disease have life-saving potential. Many of these patients will ultimately develop CHF, a common endstage of most cardiovascular conditions.

The mortality rates are high, particularly for patients who have more severe degrees of CHF. One-year mortality in severe failure may be as high as 40% to 50% (2). This fact underscores the importance of mortality as an endpoint in evaluation of therapeutic agents. It also suggests that any treatment that can delay the progression of mild failure is worthwhile.

The overall objective of treating patients with CHF is to alleviate the symptoms which often limit the functional capacity of the patients and to change the course of the condition by preventing or postponing complications including premature death.

METHODOLOGY

It should be noted that digitalis and diuretics, the mainstay of treatment of CHF, have not been properly evaluated in this patient population. There are even questions now regarding potentially detrimental effects of these agents in certain sub-groups of patients.

As in other fields of medicine, most earlier trials do not meet today's methodological standards. In fact, the majority of reports in the literature are case series. Patients are examined before and during treatment and the observed differences attributed to the drug under study. Such uncontrolled studies are of interest during the exploratory phase of drug development, but do not help in the evaluation of efficacy.

The major limitations of the randomized trials include:

1. Improper designs (e.g. cross-over)
2. Inadequate sample sizes (low statistical power to detect meaningful effects)
3. Short evaluation periods (rarely more than 3 months)
4. Fixed doses (rather than adjustable)
5. Non-optimal patient selection
6. Narrow selection of outcome measures (focus on hemodynamics rather than patient status)
7. Failure to address the preventive aspect of treatment
8. Multiple comparisons

FINDINGS

In general, the drugs that reach the clinical trial stage have a favorable effect of the physical functioning. Changes have usually been shown in the N.Y.H.A. functional class or in exercise performance. Few, if any, trials have yet considered other outcomes highly relevant to the patient, e.g. activity of daily living, social and emotional functioning, perceptions of

satisfaction and well-being. Moreover, there are few good trials in which different therapies are compared and drug combinations evaluated. With a few recent exceptions, the trials have not been designed to determine the effect of therapy on survival. The completed trials have been too small and of too short duration. To overcome this limitation and to obtain information needed for the planning of two large NHLBI-sponsored trials, Furberg and Yusuf (1,3) pooled the mortality data from trials of vasodilator and inotropic agents. There is nothing reported in the literature to support that inotropes prolong life in CHF patients. Based on two recent overviews of CHF trials (1,3) there is promise in the two ACE-inhibitors, captopril and enalapril. Moreover, Cohn et al. (4) recently reported a favorable treatment effect on mortality in their prominent placebo-controlled trial of the combination dinitrate and hydralazine.

CONCLUSION

It is obvious that better designed and larger trials are needed. In addition to examining short term treatment effect on hemodynamic variables, the impact on the patient and his ability to function in a broad sense ought to be considered. Several new large-scale mortality trials are underway or being planned and these will determine with greater certainty whether the poor progress of CHF can be altered. An important feature of the Studies Of Left Ventricular Dysfunction (SOLVD) relates to the time of initiation of treatment (primary versus secondary prevention). The experience from other areas in cardiology indicate that prevention is more effective if initiated earlier in the course of a disease. The prevention component of SOLVD will determine if an ACE-inhibitor given to basically asymptomatic patients with a low ejection fraction improves prognosis and postpones the development of overt

failure.

References

1. **Furberg CD, Yusuf S.** Effect of vasodilators on survival in chronic congestive heart failure. Am J Cardiol 1985;55:1110-1113.
2. **Franciosa JA, Wilen M, Ziesche S, Cohn J.** Survival in men with severe chronic left ventricular failure due to either coronary heart disease or idiopathic dilated cardiomyopathy. Am J Cardiol 1983;51:831-836.
3. **Furberg CD, Yusuf S.** Effect of drug therapy on survival in chronic heart failure. Adv Cardiol 1986;34:124-130.
4. **Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B.** Effect of vasodilator therapy on mortality in chronic congestive heart failure. N Engl J Med 1986;314:1547-1552.

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HOW TO STUDY SUDDEN CARDIAC DEATH AS AN ENDPOINT IN CONGESTIVE HEART FAILURE TRIALS

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SUDDEN DEATH IN HEART FAILURE

Heart failure is a common problem affecting as many as two million Americans and as many as 200,000 die annually (1). The prevalence of heart failure seems to be increasing as the prevalence of stroke and myocardial infarction decreases. Patients referred to programs specializing in heart failure have a mortality rate of about 50% in the first year of follow-up. Recently, we reviewed 13 studies of mortality in heart failure and found that 48% of 1491 patients died during a follow-up that averaged slightly over one year (2). In these studies, the fraction of deaths that are sudden, i.e., were thought to occur within one hour of terminal symptoms, was about 45%. The reports of such a large proportion of deaths that are sudden has led to the speculation that many of these deaths are caused by ventricular arrhythmias. Also, awareness that so many deaths are sudden in patients with heart failure has led to speculation that treatment that is effective in controlling arrhythmias will reduce mortality. These speculations have yet to be proven.

UNSUSTAINED VENTRICULAR TACHYCARDIA IN HEART FAILURE

Several small studies have reported the prevalence of unsustained ventricular tachycardia (VT) in patients with heart failure as detected by a single 24-hour continuous ECG recording (Table 1). None of the studies had more than 100 patients, but altogether 389 patients were included (3-9). Most of the studies were restricted to patients with New York Heart Association Class III or IV. The prevalence of unsustained VT varied from 25% to 80% in these studies; the median proportion of patients with unsustained VT was 50% and most of the individual studies were close to the median. The degree of agreement for the

prevalence of unsustained VT in patients with heart failure is striking considering the variability among the studies in terms of etiologic heart disease, severity of disease at baseline and treatment. Also, the prevalence is very high, i.e., five times as high as that found in patients at about the time of hospital discharge after myocardial infarction. It was of interest that, in each study, the mortality was substantially higher in patients who had unsustained VT compared to those who did not; the risk ratio varied from 1.3 to 5.4 and averaged about 3.0. That is, patients with unsustained VT were three times as likely to die when compared to patients without VT.

TABLE 1. Effect of Unsustained Ventricular Tachycardia on Mortality in Patients with Symptomatic Heart Failure

Author	Number of Patients	Average Follow-up (Months)	Mortality Rate		Risk Ratio
			VT Present	VT Absent	
Wilson	77	12	64%	50%	1.3
Huang	35	34	14%	7%	2.0
Unverferth	69	12	60%	28%	2.1
Chakko	43	16	36%	13%	2.8
Meinertz	74	11	39%	13%	3.0
van Olshauser	60	12	20%	6%	3.3
Holmes	31	14	59%	11%	5.4

ARE VENTRICULAR ARRHYTHMIAS INDEPENDENTLY ASSOCIATED WITH DEATH?

Until recently, the relationships among ventricular arrhythmias, left ventricular dysfunction or heart failure and death were poorly understood. The picture has been clarified for patients with coronary heart disease and previous myocardial infarction. In 1984, two multi-center studies reported analyses of the relationships among left ventricular dysfunction, ventricular arrhythmias and mortality after myocardial infarction. The Multicenter Post Infarction Program (MPIP) reported their findings in 766 patients and the Multicenter Investigation of the Limitation of Infarct Size (MILIS) reported a 533 patient study (10,11). Both studies performed a radionuclide left ventricular ejection fraction (LVEF) and a 24-hour continuous ECG recording prior to hospital discharge after myocardial infarction. Both studies used sensitive and specific computer methods to analyze the 24-hour ECG recordings. Both MILIS and MPIP found that left ventricular dysfunction and ventricular arrhythmias are not strongly related to each other, and both were strongly and independently associated with

death during follow-up. Since the risk of dying in the years after myocardial infarction is independently increased by left ventricular dysfunction and ventricular arrhythmias, their risk ratios are multiplied to obtain overall mortality. For example, if the odds ratio for dying given the presence of arrhythmias is 3.0 and the odds ratio for left ventricular ejection fraction is 4.0, the likelihood of dying when both factors are present is 12 times that of a group with neither risk factor. There are no large, unbiased prospective studies that measure ejection fraction and 24-hour continuous ECG recordings, to address the relationships among left ventricular dysfunction, ventricular arrhythmias and mortality in patients with heart failure. The seven studies shown in Table 1 are truncated samples, i.e., only patients with New York Heart Functional Class III or IV were enrolled and followed. Thus, every study showed that unsustained VT increased the mortality rate substantially when consideration is limited to a group with severe heart failure. This finding suggests strongly that the association between unsustained VT and death is independent of the clinical severity of heart failure.

IS SUDDEN CARDIAC DEATH A USEFUL ENDPOINT?

If sudden cardiac death could be equated with arrhythmic death, then this endpoint could be used to infer the effect of treatment on arrhythmias and arrhythmic death. Unfortunately, neither sudden cardiac death nor arrhythmic death in the Hinkle-Thaler classification have been validated. The ability of left ventricular ejection fraction to predict mortality from myocardial failure has not been validated either.

We encountered difficulty in attempting to classify deaths by mechanism in the MPIP, e.g., attributing deaths to heart failure, arrhythmias or ischemic events. The MPIP study is probably as representative of all hospitals in the United States as any study since the participating hospitals were widely dispersed geographically and included both university and community hospitals (12). During an average of 31 months of follow-up after myocardial infarction, 143 deaths occurred. Carefully designed mortality forms were used to collect information on the location of death, time between the onset of symptoms in the terminal event and death, and whether symptoms suggesting ischemia were present during the terminal event. For each death, it was noted whether the terminal event was witnessed. The forms were supplemented by narrative summaries written by the nurse coordinator and principal investigator in the center where the death occurred. Mortality information was reviewed on a regular basis by a four man expert committee.

To assign a mechanism to each death, the classification by Hinkle and Thaler (13) was used (see Table 2). The major categories in this classification are arrhythmic death, death due to circulatory failure and deaths that are not classifiable as being arrhythmic or the result of circulatory failure. The definition of arrhythmic death in the Hinkle and Thaler classification is "abrupt loss of consciousness and disappearance of pulse without prior collapse of the circulation". Arrhythmic deaths are further subclassified on the basis of their relationship to heart failure: (1) not preceded by congestive heart failure; (2) preceded by chronic congestive heart failure that was not disabling; and (3) preceded by chronic congestive heart failure that was disabling. The definition of death in circulatory failure is "gradual circulatory failure and

collapse of the circulation before disappearance of the pulse". The category of death in circulatory failure was subdivided into two subclasses: (1) failure of peripheral circulation; and (2) myocardial failure. Category III, not classifiable, includes death due to cancer, cerebral emboli, accidents, suicide, and complications of procedures.

TABLE 2. **Hinkle-Thaler Classification of Deaths after Myocardial Infarction**

		Number of Deaths
I.	**Arrhythmic Deaths**	
1.	not preceded by heart failure	26
2.	preceded by heart failure, not disabling	26
3.	preceded by heart failure, disabling	28
	Subtotal	80
II.	**Circulatory Failure Deaths**	
1.	peripheral circulatory failure	0
2.	myocardial failure	28
	Subtotal	28
III.	**Not classifiable**	35
	Total	143

Of the 143 deaths in the MPIP, 53% occurred outside hospital, 42% in hospital and 5% in emergency rooms. Death was witnessed in 70% of the cases and unwitnessed in 30%. Almost 25% of the deaths were not cardiac. Of the 104 cardiac deaths for which time from onset of symptoms was known, 43% were sudden, i.e., occurred less than one hour after the onset of the terminal symptom complex. Classified by the Hinkle-Thaler classification, 56% of the deaths were arrhythmic, 20% occurred in myocardial failure and 24% were not classifiable into either the arrhythmic or the myocardial failure categories. The subgroups of arrhythmic deaths are shown in Table 2. About one-third of arrhythmic deaths were not preceded by heart failure, and one-third were preceded by disabling heart failure. Nevertheless, by definition, even those deaths that were preceded by disabling heart failure were abrupt and occurred without prior evidence of circulatory collapse. Of the sudden deaths (< 1 hour), 98% were classified as arrhythmic by the Hinkle-Thaler classification. Interestingly, 54% of the non

sudden cardiac deaths were classified as arrhythmic by the Hinkle-Thaler classification.

COMPETING RISKS AND THE VALIDITY OF SUDDEN DEATH

Multiple mechanisms for death

When case finding is done by identifying patients with symptomatic heart failure, the patients are seen late in their disease when many pathophysiologic complexities already exist. Patients with ischemic heart disease represent about two-thirds of the patients with congestive heart failure. Fortunately, we have a better longitudinal view of patients with coronary heart disease because several large studies have followed these patients after an index infarct. In MPIP, an unbiased sample of patients was enrolled, characterized by objective tests designed to detect arrhythmias (24-hour continuous ECG recording), left ventricular dysfunction (radionuclide ventriculogram), and ischemia (treadmill exercise), and followed two to four years. Also, the deaths were carefully studied and an attempt was made at the local level and by the expert committee to determine the mechanism of death in terms of arrhythmias, left ventricular dysfunction, and ischemia. Indexing the population to a myocardial infarct rather than the clinical occurrence of heart failure provides a longer and broader view of the pathophysiological factors that lead to death. The first important point is that patients usually have multiple functional deficits as they approach the time of death. Many have both arrhythmias and heart failure and about half have either angina pectoris or recurrent myocardial infarction in the last few weeks of life. How these three important mechanisms interact pathophysiologically to lead to death is almost impossible to determine. A single functional mechanism of death usually can not be identified even when a patient with coronary heart disease dies in an intensive care unit with continuous electrocardiographic and hemodynamic monitoring.

Competing risks

Because several pathophysiologic factors are operating as the patient with coronary heart disease approaches death, it may be difficult to link baseline mechanism indicators, e.g., spontaneous arrhythmias, left ventricular dysfunction, or ischemic indicators, to the mechanism for death. The concept of competing risk is important in considering this problem. If we assign one primary mechanism to the deaths, a post infarction patient who has substantial arrhythmic risk (i.e., frequent and repetitive ventricular premature depolarizations in a baseline 24-hour ECG recording) may suddenly develop a fissure in a coronary atherosclerotic plaque, thrombose the vessel and die. He may die suddenly of an arrhythmia during the first moments of severe myocardial ischemia or a few days later of myocardial failure due to the added insult of yet another infarct. If the death is viewed by the experts as primarily due to heart failure or ischemia, this will represent a case in which arrhythmic risk was detected on baseline examination after the first infarct but the death was not arrhythmic. Had the fatal infarct not occurred, the patient may have died an arrhythmic death at some later point in time, but we can never know. This competing risk concept makes it clear why it may be difficult to validate mechanistic classifications of death. The major way of validating a mechanistic classification is by relating the mechanism of death assigned by a panel of experts (with all their biases) to the baseline tests used to evaluate functional components of risk (with all their shortcomings).

Validation of sudden death

One way of validating sudden or arrhythmic death would be to find a stronger association between arrhythmias detected at baseline and sudden or arrhythmic death. Similarly, the classification of myocardial failure death could be validated by finding that left ventricular ejection fraction at baseline was more strongly associated with failure deaths than with other mechanisms. So far, this form of validation for sudden or arrhythmic death is missing. Patients with spontaneous ventricular arrhythmias at baseline are not much more likely to die from sudden or arrhythmic mechanisms than from other mechanisms. Contrary to expectation, patients with low ejection fractions at baseline are more likely to die of sudden arrhythmic deaths than of myocardial failure. This lack of validity for the classification of sudden death could be due to misclassification of mechanism of death, to a shortcoming in the baseline tests in terms of their ability to characterize important functional abnormalities, or to confounding by competing risks. Whatever the reason for lack of validation for the classifications of sudden or arrhythmic death, we should not have much confidence in our ability to determine the mechanism of death.

USE OF SUDDEN DEATH TO INFER TREATMENT EFFECTS

The problem with the validity of sudden death will cloud the interpretation of studies that show treatment effects on sudden or arrhythmic death. Other factors could strengthen the inference that a reduction in deaths in the category of sudden or arrhythmic death really indicates an effect on lethal arrhythmias. For example, the likelihood of misinterpretation would be reduced if the treatment reduces arrhythmias and known arrhythmogenic factors as well as sudden death. For example, if converting enzyme inhibitors not only reduce sudden death as classified by investigators and endpoints committees, but also decrease arrhythmias in 24-hour continuous ECG recordings, reduce plasma norepinephrine and correct electrolyte abnormalities, e.g., hypokalemia and hypomagnesemia, we will have more confidence that treatment with these agents is having a beneficial effect on arrhythmias.

There is another risk of using sudden death as an endpoint for antiarrhythmic drug trials in patients with heart failure that we have not discussed yet. Treatment could reduce sudden death, but increase non sudden death, e.g., heart failure deaths, so that the net effect on mortality is negligible.

USE OF PATIENTS WITH HEART FAILURE FOR TRIALS WITH ANTIARRHYTHMIC DRUGS

The high prevalence of ventricular arrhythmias and the high mortality in patients with heart failure make them an attractive group for trials with antiarrhythmic drugs. Screening should be very efficient in this group because a large fraction of patients screened for arrhythmias using 24-hour recordings or electrophysiologic studies will qualify for antiarrhythmic treatment. However, there may be problems with using heart failure populations for antiarrhythmic drug trials. There is a growing body of evidence to suggest that it is more difficult to suppress arrhythmias in patients with low ejection fractions, e.g., <30%, or a clinical heart failure syndrome. Also, heart failure patients may experience more adverse effects during treatment with antiarrhythmic drugs. The distribution and elimination of antiarrhythmic drugs often is altered in a way that tends to increase the plasma drug

concentration on a given dose; this increases the chance of concentration related toxicity (14). Also, the probability of arrhythmia aggravation by antiarrhythmic drugs is increased in patients with low ejection fraction or clinical heart failure (15). Finally, aggravation of heart failure by certain drugs is much more likely and more important when treating arrhythmias in heart failure populations. Therefore, it is not clear that the benefit/risk ratio is favorable for antiarrhythmic drug treatment in patients with heart failure. Because of these potential problems, most physicians lack enthusiasm for treatment of ventricular arrhythmias in heart failure patients even though they believe that these arrhythmias increase the chance of dying arrhythmic deaths. Similar reservations apply to starting clinical trials in heart failure populations to determine if antiarrhythmic drugs can reduce sudden or total mortality. We need larger, unbiased evaluations of the significance and mechanisms of ventricular arrhythmias in heart failure. Also, more pilot data on efficacy, safety, dosing and monitoring therapy need to be collected and analyzed before proceeding with antiarrhythmic drug trials in heart failure patients. Ultimately, however the problem of arrhythmias in heart failure patients must be addressed.

REFERENCES

1. Francis, G.S. Development of arrhythmias in the patient with congestive heart failure: pathophysiology, prevalence and prognosis. Am. J. Cardiol. **57**: 3B-7B, 1986.
2. Bigger, J.T. Jr. Why patients with congestive heart failure die: arrhythmias and sudden cardiac death. Circulation. In press.
3. Wilson, J.R., Schwartz, J.S., Sutton, M.S-J., Ferraro, N., Horowitz, L.N., Reichek, N. and Josephson, M.E. Prognosis in severe heart failure: relation to hemodynamic measurements and ventricular ectopic activity. J. Am. Coll. Cardiol. **2**: 403-410, 1983.
4. Von Olshausen, K., Schafer, A., Mehmel, H.C., Schwartz, F., Senges J. and Kubler, W. Ventricular arrhythmias in idiopathic dilated cardiomyopathy. Br. Heart J. **51**: 195-201, 1984.
5. Huang, S.K., Messer, J.V. and Denes, P. Significance of ventricular tachycardia in idiopathic dilated cardiomyopathy: observations in 35 patients. Am. J. Cardiol. **51**: 507-512, 1983.
6. Chakko, C.S. and Gheorghiade, M. Ventricular arrhythmias in severe heart failure: incidence, significance, and effectiveness of antiarrhythmic therapy. Am. Heart J. **109**: 497-504, 1985.
7. Meinertz, T., Hofman, T., Kasper, W., Treese, N., Bechtold, H., Stienen, U., Pop, T., Leitner, E.-R.V., Andersen, D. and Meyer, J. Significance of ventricular arrhythmias in idiopathic dilated cardiomyopathy. Am. J. Cardiol. **53**: 902-907, 1984.
8. Holmes, J., Kubo, S.H., Cody, R.J. and Kligfield, P. Arrhythmias in ischemic and non-ischemic dilated cardiomyopathy: prediction of mortality by ambulatory electrocardiography. Am. J. Cardiol. **55**: 146-151, 1985.
9. Unverferth, D.V., Magorien, R.D., Moeschberger, M.L., Baker, P.B., Fetters, J.K. and Leier, C.V. Factors influencing the one-year mortality of dilated cardiomyopathy. Am. J. Cardiol. **54**: 147-152, 1984.
10. Bigger, J.T., Jr., Fleiss, J.L., Kleiger, R., Miller, J.P., Rolnitzky, L.M. and The Multicenter Post-Infarction Group. The relationship between ventricular arrhythmias, left ventricular dysfunction and mortality in the 2 years after myocardial infarction. Circulation **69**: 250-258, 1984.
11. Mukharji, J., Rude, R.E., Poole, W.K., Gustafson, N., Thomas, L.J., Jr., Strauss, H.W., Jaffe, A.S., Muller, J.E., Roberts, R., Raabe, D.S., Jr., Croft, C.H., Passamani, E., Braunwald, E., Willerson, J.T. and the MILIS Study Group. Risk factors for sudden death after acute myocardial infarction: two year follow-up. Am. J. Cardiol. **54**: 31-36, 1984.
12. The Multicenter Postinfarction Research Group. Risk stratification and survival after myocardial infarction. N. Engl. J. Med. **309**: 331-336, 1983.
13. Hinkle, L.E., Jr. and Thaler, H.T. Clinical classification of cardiac deaths. Circulation **65**: 457-464, 1982.
14. Woosley, R.L., Echt, D.S. and Roden, D.M. Effects of congestive heart failure on the pharmacokinetics and pharmacodynamics of antiarrhythmic agents. Am. J. Cardiol. **57**:25B-33B, 1986.
15. Morganroth, J., Anderson, J.L., Gentzkow, G.D. Classification by type of ventricular arrhythmias predicts frequency of adverse cardiac events from flecainide. J. Am. Coll. Cardiol. **8**:607-615, 1986.

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Interpretation of Clinical Trials in Patients with Congestive Heart Failure

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The general principle of clinical trials hold in clinical trials of congestive heart failure as in other clinical areas.[1-2] This article will not review these general principles, but will touch upon a few points particularly applicable to drug trials in congestive heart failure. In preparation of this paper the trials referenced in the editorial by Furberg and Yusuf[3] as well as some others found by examining the literature were reviewed. These trials[4-26] generated the following comments.

Heterogeneity of Patient Groups

There is great heterogeneity in prognosis among patients with congestive heart failure (CHF).[27] Both patient symptoms and quantitative measurements add independent prognostic information. The strong gradients in clinical outcome make nonrandomized control groups of dubious benefit. Randomized clinical trials are even more important here than in most areas.

Two operational points have neglected in a few randomized trials in this area. First, it is important that those randomizing patients do not know the sequence of assignments; otherwise patients may be selectively enrolled -- resulting in a biased distribution of patients between the groups. Second, randomization should take place at the last possible moment. There is, or may be, a difference between the time of enrollment in a study and the time of randomization. For example, if there is a single blind placebo run in period the patients should be enrolled in the study before the run in period, but randomized after the run in period when active drug is randomly assigned. In this way patients dropping out before the run in period is over do not complicate the randomized comparison. Or again consider a randomized trial where each patient is first dose ranged on an active drug. After dose ranging patients are then randomized to active drug at the dose from the preliminary dose ranging or to placebo. Patients would be enrolled in the study before the preliminary dose ranging on active drug; that experience would of course be considered in evaluation of safety. The randomization would not take place until the second phase of the study began. Thus individuals showing no (presumed) drug effects, intolerant of the drug, or dropping out in the first dose ranging phase would not add "noise" to the randomized therapeutic comparison.

While perhaps overstated, I would suggest that if a placebo is not unethical, it is unethical not to use a placebo. Note that this placebo and active drug may be compared on a base of other drugs, for example, digitalis and diuretics. Active control trials give many difficulties.[28-30] What are "equivalent" doses? How does one show drugs are equivalent in effect?

Hypothesis to Tested

Except for initial studies a clearly formulated hypothesis is needed to design a study allowing a clear conclusion. A number of factors need to be considered.

A number of possible endpoints from least to most important are possible: hemodynamic/physiologic; clinical status; quality of life; need for dramatic intervention (e.g., heart transplant); and mortality. Many statisticians, including the author of this paper, believe an intent-to-treat analysis should always be one analysis done in a randomized study. (An intent-to-treat analysis includes all individuals randomized in the analysis; they are included in the group to which they are randomized.) Note deaths and drop outs would then be included in the analysis; this will often involve a nonparametric statistical analysis treating deaths as the worst possible outcome for example.

If an intermediate endpoint such as exercise testing is used to reflect quality of life, strong documentation must link the intermediate endpoint as a measure of the inferred other result. The duration of follow-up has been short in most studies, (the recent Veterans Administration study[8] being an exception.) Studies of 2 or 3 months have been called long term follow-up. Perhaps intermediate follow-up would be a more appropriate term. The mortality in CHF is among the highest in cardiology diagnoses. It is surprising more studies using all cause mortality as the endpoint of interest have not been performed.

Cross-over studies are perhaps less useful in CHF than in some other areas. Deaths may complicate long term cross-over studies; the clinical course may change making the portions of the cross-over design not comparable; often the clinical course is quite variable making the gain in statistical power limited.

The hypothesis should test a clinically relevant application of the drug. If dose ranging is considered essential in practice it should be used in the clinical trial. Note that dose ranging with placebo is possible and has been done.

Patient selection criteria need especially careful definition because of the strong prognostic gradients with the patient groups. The etiology may be important for some drugs; for example possible autoimmune disease in some CHF of cardiomyopathy.

Other Issues

A number of other issues are worthy of consideration. The paper closes with miscellaneous points.

The multiple comparison problem arises when many statistical tests, or comparisons, are examined at once. If each hypothesis is tested at a 0.05 significance level and all the null hypotheses are true the probability of one or more statistically significant findings is far greater than 0.05. Particular difficulty arises when measures go in opposite directions. Two ways to deal with this problem are: 1.) defining a few a priori important statistical tests upon which the interpretation of the study results will depend; or 2.) a planned system for combining different measurements. Exploratory studies measuring many outcome variables without predetermined analysis plans are difficult to use to prove efficacy unless all the variables strongly support the finding; these problems should be avoided.

The potential long term tolerance to some drugs for CHF must be dealt with, presumably usually with follow-up.

References

1. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. USA: John Wright PSG Inc., 1981.

2. Meinert CL. Clinical Trials Design Conduct and Analysis. New York: Oxford University Press, 1986.

3. Furberg CD, Yusuf S. Effect of Vasodilators on Survival in Chronic Congestive Heart Failure. Amer J of Cardiol 1985;55: 1110-1113.

4. Aronow WS, Greenfield RS, Alimadadian H, Dahahy DT. Effect of the Vasodialtor Trimazosin Versus Placebo on Exercise Performance in Chronic Left Ventricular Failure. Amer J of Cardiol 1977;40:789-793.

5. Bayliss J, Norell MS, Canepa-Anson R, Reid C, Poole-Wilson P, Sutton G. Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. Br Med J 1985;290:1861-65.

6. Cleland GF, Dargie HJ, Hodsman GP, Ball SG, Robertson JIS, Morton JJ, East BW, Robertson I, Murray GD, Gillen G. Captopril in heart failue A double blind controlled trial. Br Heart J 1984;52:530-5.

7. Cleland GF, Dargie HJ, Ball SG, Gillen G, Hodsman GP, Morton J, East BW, Robertson I, Ford I, Robertson JIS. Effects of enalapril in heart failure: a double-blind study of effects on exercise performance, renal function, hormones, and metabolic state. Br Heart J 1985;54:305-12.

8. Cohn JN, Archibald DG, Ziesche S, Franciosa JA, Harston WE, Tristani FE, Dunkman WB, Jacobs W, Francis GS, Flohr KH, Goldman S, Cobb FR, Shah PM, Saunders R, Fletcher RD, Loeb HS, Hughes VC, Baker B. Effect of Vasodialtor Therapy on Mortality in Chronic Congestive Heart Failure (Results of a Veterans Administration Cooperative Study*). N Engl J Med 1986;314:1547-52.

9. Colucci WS, Wynne J, Holman BL, Braunwald E. Long-Term Therapy of Heart Failure with Prazosin: A Randomized Double Blind Trial. Amer J of Cardiol 1980;45:337-44.

10. Conradson TB, Ryden L, Ahlmark G, Saetre H, Persson S, Nyquist O, Wernersson B. Clinical efficacy of hydralozine in chronic heart failure: one-year double-blind placebo - controlled study. Amer Heart J 1984;108:1001-6.

11. Dibianco R, Shabetai R, Silverman BD, Leier CV, Benotti JR. Oral Amrinone for the Treatment of Chronic Congestive Heart Failure: Results of a Multicenter Randomized Double-Blind and Placebo Controlled Withdrawl Study. JACC 1984;4:855-66.

12. Franciosa JA, Wilen MM, Jordan RA. Effects of Enalapril, a New Angiotensin-Converting Enzyme Inhibitor, in a Controlled Trial in Heart Failure. JACC 1985;5:101-7.

13. Glover DR, Wathen CG, Murray RG, Petch MC, Muir AL, Littler WA. Are the clinical benefits of oral prenalterol in ischaemic heart failure due to beta blockade? A six month randomised double blind comparison with placebo. Br Heart J 1985;53:208-15.

14. Higginbotham MB, Morris KG, Bramlet DA, Coleman RE, Cobb FR. Long-Term Ambulatory Therapy with Prazosin Versus Placebo for Chronic Heart Failure: Relation Between Clinical Response and Left Ventricular Function at Rest and During Exercise. Amer J of Cardiol 1983;52:782-88.

15. 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.

16. Leier CV, Huss P, 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.

17. McGrath BP, Arnolda L, Matthews PG, Jackson B, Jennings G, Kiat H, Johnston CI. Controlled trial of enalapril in congestive cardiac failure. Br Heart J 1985;54:405-14.

18. Markham RV, Corbett JR, Gilmore A, Pettinger WA, Firth BG. Efficacy of Prazosin in the Management of Congestive Heart Failure: A 6 month randomized, double-blind, placebo controlled study. Amer J of Cardiol 1983;51:1346-52.

19. Massie B, Bourassa M, DiBianco R, Hess M, Konstam M, Likoff M, Packer M. Long-term oral administration of amrinone for congestive heart failure: lack of efficacy in a multicenter controlled trial. Circulation 1985;71:963-71.

20. Mettauer B, Rouleau JL, Bichet D, Kortas C, Manzini C, Tremblay G, Chatterjee K. Differential long-term intrarenal and neurohormonal effects of captopril and prazosin in patients with chronic congestive heart failure: importance of initial plasma renin activity. Circulation 1986;73:492-502.

21. Murphy J, Coxon R, Sharpe DN. Practical aspects of clinical trials: A review of a randomized, placebo-controlled study in patients with heart failure. Heart & Lung 1985;14:95-100.

22. Pehrsson SK. Multicentre Comparison Between Slow-Release Furosemide and Bendroflumethiazide in Congestive Heart Failure. Eur J Clin Pharmacol 1985;28:235-39.

23. Sagar S, Sharma BK, Sharma PL, Wahi PL. A comparative randomized double-blind clinical trial of bumetanide and furosemide in congestive cardiac failure and other edema states. Int J of Clinical Pharmacol 1984;22:473-78.

24. Sharpe DN, Murphy J, Coxon R, Hannan SF. Enalapril in patients with chronic heart failure: a placebo-controlled, randomized, double-blind study. Circulation 1984;70:271-78.

25. Todd PA, Heel RC. Enalapril A Review of Its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Use in Hypertension and Congestive Heart Failure. Drugs 1986;31: 198-248.

26. Weber KT, Kinasewitz GT, West JS, Janicki JS, Reichek N, Fishman AP. Long-Term Vasodilator Therapy with Trimazosin in Chronic Cardiac Failure. N Engl J Med 1980;30:242-50.

27. Fisher LD, Alderman EL, Mock MB, Chaitman BR, Ringqvist I, Ryan TJ, Levine F, Kaiser GC, Schloss M, Killip T, Oberman A, Litwin P. Statistical considerations in evaluating treatment of advanced congestive heart failure. In Congestive Heart Failure (Braunwald E, Mock MB, Watson JT, eds). Grune & Stratton, 1982, 357-66.

28. Temple R. Difficulties in Evaluating Positive Control Trials. Amer Stat Assoc 1983 Proceedings of the Biopharmaceutical Section, pp. 1-7.

29. Lamborn KR. Some Practical Issues and Concerns in Active Control Clinical Trials. Amer Stat Assoc 1983 Proceedings of the Biopharmaceutical Section, pp. 8-11.

30. Hsu J-P. The Assessment of Statistical Evidence from Active Control Clinical Trials. Amer Stat Assoc 1983 Proceedings of the Biopharmaceutical Section, pp. 12-16.

DISCUSSION - 5

Dr. Moore: Dr. Fisher said that placebo's are not ethical; is it unethical not to use a placebo in a clinical trial? What is your thought concerning that?
Dr. Fisher: The statement was if placebos are not unethical, using the double negative for the purpose of having the second phrase be symmetric, then it is unethical not to use a placebo.
Dr. Furberg: It depends how you set up the trial. I think the most important consideration in the trial should be the patient and we should give whatever the optimal therapy is, and then on top of that we do our placebo control group.
Dr. Yusuf: I think the extreme example is the patient in class IV failure. I think even there you could do a placebo control trial. You use whatever standard therapy like IV Lasix, digoxin or even IV nitrates for instance and then you have something on top of that and that could be placebo controlled. So long as you give whatever is needed to control symptoms and/or whatever is the immediate gain of therapy, there is no real ethical dilemma. I agree with Dr. Furberg.
Dr. Maroko: Dr. Fisher, would you consider a patient who was in ventricular fibrillation, that needed defibrillation at the same category similarly as the heart transplant? If a patient had a ventricular fibrillation that needed a defibrillation, and otherwise would die, if there would be no acute medical treatment.
Dr. Fisher: I would accept that as an adequate endpoint. For example, if somebody had a trial and (at least there is one going now with implantable defibrillators for an antiarrhythmic) if a patient experienced VF and it was documented, that certainly would be equivalent. I don't know of any, but somewhere somebody has seen somebody spontaneously convert from VF, but it must be phenomenonly rare. Dr. DiBianco: We have heard the suggestion of a possible study design that would include an early test dose or short dose ranging before patients were randomized and I was wondering what Dr. Temple's and Dr. Fisher's thoughts and other panelists as well as to does this allow the investigator group to somehow select out those patients who might be biasing the sample in favor of the drug because it will take out those patients who don't show a very favorable early response.
Dr. Temple: I don't think it keeps the study as performed from giving an answer. The questions you would raise pertain to how generalizeable it is and that may or may not be a problem. If you found that 50% of all people in a particular category could not be put onto a beta blocker successfully, then you would know that from the initial screening and then you would have a conclusion about the people who could be put onto them successfully and it seems to me you would know most of what you want to know. There are situations in which you lose certain information about generalizeabilty, but I think the conclusion that gets derived from the study you actually carry out is perfectly valid. I don't see any bias in it.
Dr. Fisher: I agree with what Bob has said. It may affect the labeling. In people who are initially dose ranged to such and such response, and so on, then there is a beneficial effect. You cannot get adequate dose range and information simply out of the people who

were successfully dose ranged. This design has been tried at least once and presented to the cardiovascular renal advisory committee and that was the only problem we ran into because by definition you have people who can get a beneficial effect for that side effect, but if you took into account, all the data of the people you try to dose range, I think you could get adequate information for labeling purposes, where to start the doses and what not.

Dr. Yusuf: I think actually it is an imminently sensible design to do that. Once you accept that it is only generalizeable to a certain point, and it is sensible because in normal clinical practice, what we would do is give the drug to the patient, and if he doesn't tolerate it, we would stop it. What we really are interested in is what happens to those who continue to tolerate it, so a running period by randomization after you issue tolerance or effective dose or whatever, makes sense. The standard trials that we have been doing where we randomize at time 0 and the people who don't take the drugs, say we have to do an intention to treat analysis and that is right, but it is an insensitive analysis because you are including the people who don't take the drug. In fact this very design but using the SOLVD study where we have a running period where the active drug is given and if people get side effects as severe hypotension or severe renal failure, clearly nobody in the world would want to treat these people long term. They are removed and then we randomize the people who don't get side effects and who tolerate the drug. I think it is an imminently sensible design.

Dr. Furberg: I agree with that but I think we have to be a little bit careful also about which response we are using to selecting our patients. If you are doing a mortality study and you select them on the basis of hemodynamic response, it could be that we are weeding out the wrong patients. We have to be sure that the ones you are eliminate are not going to benefit and that the response you are selecting among is related to the outcome in the full scale trial.

Dr. Temple: That is true, but then the drug doesn't prove effective, but normally, for example, if you thought you had a drug that improved ventricular function in a subset, and you want to look at mortality, there is obviously a relationship and that would be why you would choose people who had improved ventricular functions.

Dr. Fisher: I think you may lose a little bit more by weeding out some patients, consider that at least in the design.

Dr. Temple: The beta blocker example suggests that. If you gave people a large test dose of beta blocker and excluded all the people who couldn't tolerate it, you might lose a lot of people you most want to treat which you could have kept in if you had started with a little test dose and then raise them up. These techniques are all a part of something in the past I have called enrichment. They are all attempts to eliminate people who will produce noise from the population. You have to keep in mind what you are doing. First of all, you may be wrong, you may not have enriched it. You may have trashed it. Secondly, you have to remember who the results are in. It is not the whole population, it is a subset of the population and of course it is easy to forget that in the triumph of the trial as it works out. You forget who you excluded so it is important to pay attention.

Dr. Yusuf: Actually you have a further refinement of the same thing. For instance, you could obviously eliminate the people who get side effects or are intolerant, but you may also want to ask yourself, are there some subsets that can be predicted based on short term response. You don't know whether that hypothesis is true or not, so you give a drug for a while, then you have some indicator of response for instance, people with good hemodynamic response. You randomize both sets of people and your a priori hypothesis is people with good hemodynamic response short term are the same ones who respond long-term and if you don't do a run in period in everybody, you only know what short term responders and the people you have randomized but you don't have in your control group the comparable patients. In fact, that has been one of the flaws in the entire area where they say acute responders versus long term responders. That is a hole in the studies that have tried to do that. Again, if you want to take some short term response index and compare it to long term, then you could stratify it that way.

Dr. McNay: I would like to ask Drs. Temple and Lipicky about that design when contrasted with the typical parallel designs with randomization, whether one would end up with difficulties on dose response?

Dr. Lipicky: I think I would respond to that the same way Dr. Temple did. If you envision the information that you want to get from a parallel group dose response study as an estimate of the general population's response, if that is the purpose of the trial and you don't do that, that is you only include people who respond in some fashion or who don't have side effects when they get to the highest dose, then you haven't answered the question, so it is an issue of generalizeability and I do believe unless there is some special reason not to have information that relates to the general population, that one would want to have that general population estimate as opposed to some refined population estimate.

Dr. McNay: If one had two goals, one is say dosage recommendations and the second is efficacy, would one say that this preselected type trial would be sufficient for efficacy.

Dr. Lipicky: It would certainly be adequate for demonstrating that the drug works in some people.

Dr. Temple: I think this is something that deserves some more discussion and thought. If you knew for example that a population was made of the people who didn't respond at all or hardly responded at all to a drug and some other people who did respond, I think you can ask which group of those people would be of more interest to get dose response information in. That of course depends on what you want to use this information for. I would put forth as a thought that you probably want to study it in the people who respond, because those are the people in which titrating the dose is going to be meaningful. People who don't respond at all, what you really need to know is there is a sub population of people who don't respond up to any dose and once you have that you know how to deal with people who responded because you know how far to go.

Dr. Fisher: I have always thought that the reason we ask for dose range information from the pharmaceutical industry was primarily to get rational labeling of how to use the drug. One of the important things is what dose do you start a drug at. Normally, you try to

find a dose where you have a relatively small proportion of the population who will have side effects and hopefully quite a bit with response. If you have a preselected population who responds, you have done away with possibly a very large number who have side effects.

Dr. Temple: But you say they didn't respond.

Dr. Fisher: No, depending upon how you do it, for example, we had an example of before the committee of where not a lot of people dose ranged but the only people included in the randomized trial because they wanted to do a crossover were people who tolerated the highest possible dose and then the sponsor wanted to use that information for dose ranging. This really doesn't work, because these are people who by definition tolerate the highest possible dose. We know we are not going to get any side effects up to the highest dose, how can you use that to decide what dose to start the general population on. In fact, if you use that population, you would start it on the highest dose they were studying because there were no side effects and you had the largest response.

Dr. Temple: I have no doubt we could discuss this for several days, but if one kept track of the initial titration that excluded people and found that at dose one, a certain number of people drop off, you would then have the information on how people get sick.

Dr. Fisher: I thought I said that, in fact they were in my very initial remarks, and if I didn't, I should have.

Dr. Temple: You need to keep track of that, but if you had that, maybe you would then have what you need to know about tolerance and could then work on the responders to get the idea of where is it sensible to start. For example, suppose you had a situation in which 90% of people don't respond to the agent, only 10% do. Of the 10% who do, only a small fraction of them respond to a dose of 1, most of them take about 5. If you look at all of that data in all of the people, the 90 who don't respond and the 10 who do, you would probably conclude that dose 1 didn't have any effect. In fact, that is a reasonable dose to start at because among the responders, a fair fraction of them respond to that dose. You would want to know that. You may get a more sensitive idea of what the dose response is if you do at least a portion of your studies in that population. I guess part of my answer is don't put all your eggs in one basket. If it is reasonable to do these enrichments, but also do a conventional study to see if there is any difference at least until all this is sorted out. That makes some sense, but I think there may be a role for both.

Dr. Yusuf: I think one of the things about a trial is generalizeability and what the estimate of effects say in a larger unselected population would be. You can actually get to that by the fact that you know what proportion of people get into the trial, what the effect there is and then you dilute that effect out by the people who don't get into the trial. There is only one problem with that and it may not be applicable to the cardiovascular field but is certainly is applicable to the cancer field, there might be some long-term toxicity of that short dosing in some people. For instance, if you treat somebody for two months with say two doses of chemotherapeutic agent and you said if they could actually tolerate and they don't get bone marrow depression I will randomize them to

continue it or not to get it. It may be that even short term treatment causes long term toxicity. A good example of this is radiation for breast cancer. In the short term, there is no effect at all but in the long term it kills women with breast cancer. That is what the data showed. We have to take each therapy and this design can have problems. It can give you misleading results at times.

Dr. Lipicky: It is indeed a problem that could be discussed for days but I wanted to add one other thought and that is that unless one performed a fixed dose titration in some general population that in fact took everyone from the smallest dose to the biggest dose, one really wouldn't have the information that some people don't respond unless indeed dose went way up and one could conclude that in fact no one responds. The business of enrichment or parallel trials did really get answered. Does everyone in a general population respond or not and indeed there are problems anyway you cut the cake and one really has to know the question that is being asked of the dose ranging trial in order to figure out what the design would be.

Dr. Cohn: I wanted to express some concern about the screening of patients for entry into efficacy trials. I am not the least bit troubled by testing patients to a drug and discontinuing and not randomizing them if they have overt side effects, that is fine. Once you begin to use the hemodynamic response to the drug as a guide to who you will put into the trial, you end up with a real problem in that you have selected the patient population by an invasive study that puts the burden then on a physician to use that criteria for entering patients onto the therapy and that is clearly not the way we take care of patients. We don't determine their response to digitalis hemodynamically before deciding whether to digitalize them and I think it is not a reasonable way to study a drug because it doesn't apply to clinical practice.

Dr. Yusuf: I think that point is very valid and I was just using that not to say that you should use hemodynamic response in every case but to say if you had an a priori hypothesis that short term response and it could be clinical response was the thing that made the difference long term and it may be that whether people just feel better, I mean N.Y. Heart Association classification, got better, you could use that to just stratify them. I will still randomize the people who don't respond as well to test my hypothesis but that is one possible use and in some situations it is unrealistic.

Dr. Cohn: I wasn't responding to your comment at all. I was responding to the fact that I have seen a number of protocols come out from pharmaceutical companies doing just exactly that, that is, testing people to their hemodynamic response to an inotropic drug and only those who got a desirable effect with a rise in output of a certain amount then get randomized into the efficacy trial. I am objecting to that approach, because I don't think we can apply that patient population to general patient care.

Dr. Morganroth: Is that because there is no relationship between acute hemodynamics and longterm end points exercise tolerance? Is that why you want to have as many patients in the efficacy trial to compare whether the acute hemodynamic effects were or were not useful for predicting a long term effect? If one looks at

antiarrhythmic trials, would you not want to know the VPC response assuming your hypothesis that antiarrhythmics work by decreasing VPC's. You wouldn't want to just take patients tolerating an antiarrhythmic and put them in an efficacy trial with the assumption that empiric antiarrhythmic drug therapy that had no effect on PVC's was going to prevent an arrhythmic event.

Dr. Cohn: I mean monitoring VPC's is within the realm of every clinician to do and that is perfectly fine. I am saying in this instance if you got this drug, the labeling for the drug would have to say, this drug can improve people who have a hemodynamic response to first dose administration of the drug and that is an unreasonable requirement for labeling. You don't want physicians out there feeling they can catheterize their patients before doing a Holter is an acceptable form.

Dr. Morganroth: If they could. The problem is Holter is easy and Swann-Ganz isn't so easy, but if you knew that a drug, could predict the Swann-Ganz measurement and that was the means of predicting long term effect, then in fact you would want the clinician to take the patient, put him in the hospital and use the Swann-Ganz measure before giving him the drug. If you knew that acute hemodynamics was a good way of predicting effect from digitalis then you would want everyone to have a Swann-Ganz measure before they receive digitalis.

Dr. Cohn: If it really were a clean separation, you would certainly have to use clinical results. I happen to personally doubt that it would be and it hasn't been with other drugs that we have looked at and we certainly don't have the data but it would put a terrible burden on physicians if that were the only way they could start therapy in their patients with modest heart failure.

Dr. Morganroth: I agree and am just arguing the principal because in heart failure it appears that the changes in acute hemodynamics do not necessarily predict at all the long term effect.

Dr. Temple: I hear a socio-practical comment rather than a scientific comment. Don't choose something that is really hard to do at least be sure that something simpler wouldn't do as well like maybe an ejection fraction response because people can do an echo relatively easily. I suppose everyone would agree if the only successful way of identifying the people who do well turned out to be something messy, then you probably want to say that is O.K. If you set it up the way that he described, then you almost guarantee that the only thing that you are going to discover as a predictor is something that is very hard to do and that's uncomfortable.

Dr. Fisher: The problem is you haven't even shown that is a predictor because those are the only people you have studied. You don't even know what would have happened to the other group. They might have done as well, so I think it is a deeper problem than that.

Dr. Yusuf: You can get around that by studying both groups.

Dr. Fisher: But then you don't have the same result.

Dr. Bigger: That is the point that I was going to make. If you are going to study both groups, you are going to have study both groups with substantial numbers such that you can make comparisons and if you think of one of the hypotheses as being sort of primary and the split is not good, so that the non-responders or the

intolerant is a small subset like 15% then you won't learn much from randomizing the 15%. It may be a trend if it is dramatic, but maybe not.

Dr. Yusuf: You have to take each situation separately.

Dr. Packer: There is an irony here and that is in trying to construct dose response curves for vasodilator therapy, almost all of the dose response data we have with vasodilators and inotrope is short term hemodynamic effects but if you say that short term hemodynamic effects don't predict long term hemodynamic effects or long term efficacy, then one seriously has to think about whether any short term dose response curves mean anything at all. I don't even mean least bit helpful. I mean totally irrelevant in trying to predict what happens and maybe the only way, the classic example is converting enzyme inhibition when these drugs were first used in the treatment of hypertension was not particularly appreciated that there were delayed responses to treatment so that long term responses that were seen were attributed to dose increments and it was thought that you needed very high doses to get the response when if you had just stayed with low doses but continued therapy for long periods of time, you would have gotten the same response and less toxicity. Therefore if you already have a precedent for the fact that the first dose doesn't mean very much, then all dose response data done during the acute study really may not mean very much in terms of planning long term trials.

Dr. Temple: The history of hypertension studies bears that out. The dose for every antihypertensive agent marketed that I know of was always wrong, often by one or two orders of magnitude. That maybe because the short term studies aren't very well done, but what you say is true. The only problem is that it is hard to do large parallel dose response studies because each group has to be pretty big. Maybe not as big as it sometimes seen if you try to use the whole dose response curve instead of just insisting on 2x2 comparisons, but still it makes for very large studies, and if you guess wrong, you have really blown it.

Dr. Lipicky: I don't disagree with anything that has been said. I am not sure that I agree with the sense of it. It is not clear that short term dose response is done in order to have long term predictive value and if indeed short term is done for that purpose it probably is some misconception because it is reasonably clear that it doesn't have predictive value, however, you can get some feeling for dose-peak effect, dose-time effect for a single dose and that information would indeed be useful from the vantage point of being able to legitimately plan what it is that one would want to look for long term to do long term dose response studies is indeed complicated if one sticks to the parallel group dose response design. I don't think there is any reason to believe that that is the best design or the only design or the only way in which one can derive that kind of information. It does indeed lead one to get group data dose response. It ignores individual responses entirely and is kind of information that is useful if you are looking at population type things where you want to have some idea of what the limits would be or randomly selected population and this has been expressed early although that information is useful, it is not the only information one would want and it has limited ability in

itself, but again to really continue all of this is a very long discussion. It is just the sense of it that I had some disagreement with.

Dr. Packer: Actually I agree with what you have said. It is not the only the way nor is it necessarily should be the required way, but there is a history in this particular field of going too high on a lot of doses and I think largely because of a reliance on short term dose response data.

Dr. Lipicky: I don't agree with that. If you look at Captopril, it was very clear that the peak effect of Captopril on blood pressure occurred at doses substantially below 10 mg. The unreasonable estimate of the useful dose really came from clinical trial information and was not really because the single dose studies led one up the wrong tree. It is hard to find in the hypertension area, adequate single dose characterization, that is not common. The single dose response characterization of antihypertensives is not information that led one down the wrong path. In fact it is missing most of the time and it is the titrated to some clinical response dose ranging trial that generally I think can be blamed for leading to the wrong dose estimate and I am not sure why that is, except empirically it has been adequately demonstrated that you get two very different answers if you do a titrated dose response, analyze the data conventionally and for the same drug do a group parallel dose response and analyze the data conventionally.

Dr. Packer: I think part of the problem is we don't know what we want. We don't know if we want a drug that increases cardiac output by 20%, 35%, or 42.7%. We want a drug that works and all the dose response characteristics is based on the concept that we know what we want short term, because that predicts what happens long term and it isn't so. Even the dose duration response short term may not apply to what happens long term. We don't know anything about the characteristic of whether you need the wedge pressure to be down at 24 hours 80% of the day, 60% of the day. We don't know any of this. The only point that I wanted to make is a lot of these assumptions are built into the initial trials that find dose response, dose duration and it is possible and very conceivable and has happened all the time that the assumptions, the conclusions drawn from these short terms studies in terms of dose response would then apply. Everyone says oh yes, the drug works, but you have a dose which is 4 times what you need. That is my only concern.

Dr. Sami: One of the problems that we have in proving any one given antiarrhythmic prolongs life is that we find if we try to treat a group of patients with any one antiarrhythmic, only 25 to at the best 30% of the patients will respond to the antiarrhythmic, tolerate it and have short term control. Then it becomes very difficult when you do randomized trial with just one single antiarrhythmic to answer the question. Aren't we going into the same kind of problem with trying to prove that any one vasodilator is going to really prolong life of a heterogeneous group of patients who respond differently to different vasodilators. One may tolerate better one group of drugs than the others. Why not ask the question, like for the antiarrhythmics, does control of the arrhythmia prolong life regardless of which antiarrhythmic we use? Using the model for example, we titrated various number of

antiarrhythmic drugs and only those who have short term response get randomized to the drug versus control. Why not ask the question, does afterload reduction prolong life and try and design something that would involve titration with more than one vasodilator. Just try to look at this hypothesis.

Dr. Temple: You could probably do that. Is the hypothesis correct though? For example, do you know that there are people who respond to one vasodilator and not another or do people tend to be responders or non-responders to the whole group. If what you say were really true, then you probably would take an approach which said O.K. my goal in the treated group is to reduce the following measurement by the following amount. I will do it with any drug or combination of drugs I can and that would be perfectly reasonable. I guess I don't have the sense where we have reached the point where that appears to be necessary unlike arrhythmias where it is plainly necessary and that is why nobody does trials with single drugs that way.

Dr. Moore: A couple brief comments and conclusions. I think Dr. Yusuf gave us the reason why there has been so much enthusiasm and interest in this meeting when he pointed out that there are about 200,000 deaths in the U.S. alone due to congestive heart failure and he also pointed out that in each of the last three decades, the number of deaths due to congestive heart failure has been increasing at an alarming rate. This certainly contrasts with what we are seeing in sudden cardiac deaths, where in a little over a decade, we have decreased the number of sudden cardiac deaths to about half of what they were in the 1950's. There is no clear reason that he could discern nor a clear reason that I could get out of these discussions as to why the number of congestive heart failure deaths are actually increasing. I think the question that we all had is how does one evaluate a drug to treat congestive heart failure? What has predictive value? It certainly came out to be a little confusing. Ejection fractions, cardiac output, they didn't correlate well. Exercise tolerance perhaps did. I think that Bob Temple came out with a comment which I thought was appropriate. You have to prove what you claim and if you live longer and you live better, maybe all you have to do is prove that. However, Dr. Lipicky came back and said he couldn't see anything that he could say today that would necessarily be true 6 months from now. The point that he was trying to make was an excellent one, and that is that we are learning so many things with each clinical trial, is that what you expect in a clinical trial is constantly changing as one has more and more information. Dr. Temple also pointed out that one doesn't have to prove the mechanism in order to approve a drug. All you have to do is prove your claim. Then he further went on to say that in order to avert any disasters, what one really needs to do is to understand mechanisms and you better learn what your problems are as early as you possibly can because the earlier you learn your problems, then the more money you are going to save or the more enthusiastic you are going to be for that new drug. I think it was particularly interesting, the comments regarding placebos. Dr. Packer pointed out that if they had stopped the Captopril trial at the end of 4 weeks, that it would not have been significant yet when they went to 12 weeks, just what the placebo

group did made it a very significant trial. They contrasted other trials. I think it was interesting to hear the differ between Dr. Cohn's experience on placebo groups and Dr. Pack experience. It really came down to the point, that if you w know what your effect of the drug is you would go out with J if you are a gambler and you are going to bet on the placebc dose, you might want to have your studies in New York becaus placebo groups can do some strange things. I know everyone to hear what are the new FDA guidelines for using new drugs congestive heart failure, and I think as Ray Lipicky and Bob mentioned, that is a two year project and I don't think that up with any definite conclusions at this time.

SYMPOSIUM ON NEW DRUGS AND DEVICES

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