JACC Vol. 13, No. 3
March 1, 1989:513–23

ACC ANNIVERSARY SEMINAR

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Changing Strategies in the Management of Heart Failure

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Forty years ago therapy for congestive heart failure was limited largely to the mercurial diuretics and a variety of cardiac glycoside preparations; these were often ineffective, and the common practice of "pushing" digitalis caused serious, sometimes lethal side effects. Today, a more complete understanding of the regulation of cardiac work and pathophysiology of heart failure is having a profound impact on therapeutic strategy for this common condition. Despite more powerful means to augment myocardial contractility and much more effective diuretics, therapy that relies only on inotropic stimulation and diuresis is no longer optimal for the majority of patients with heart failure. Thus, strategies for the therapy of heart failure must take into account new understanding of mechanisms that initiate, perpetuate and exacerbate the hemodynamic and myocardial abnormalities in these patients.

Recognition of the detrimental effects of excessive afterload and the importance of relaxation (lusitropic) as well as contraction (inotropic) abnormalities has led to widespread acceptance of vasodilator therapy, which has dramatically improved our ability to alleviate the symptoms of heart failure. Changes that result from altered gene expression in the hypertrophied myocardium of patients with congestive heart failure can give rise to a cardiomyopathy of overload that, although initially compensatory, may hasten death. These and other advances in our understanding of the pathophysiology, biochemistry and molecular biology of heart failure provide a basis for new therapeutic strategies that can slow the progressive myocardial damage that causes many of these patients to die, while at the same time improving well-being in patients with congestive heart failure.

(J Am Coll Cardiol 1989;13:513–23)

"The heart muscle supplies the force which maintains the circulation. In the normal condition, the mechanism of the circulation is so adjusted that all parts combine to facilitate the work of the heart and to attain the object of the circulation. Any disturbance of that adjustment must at once entail more work upon the heart muscle, inasmuch as a departure from the normal means the embarrassment of the heart in maintaining normal arterial pressure. So long as the heart can overcome the impediment, and maintain the circulation in a normal manner, no symptoms are evoked, but if the heart is no longer able to carry on the circulation efficiently, then certain phenomena at once arise, and these phenomena we call 'symptoms of heart failure.' "

Sir James MacKenzie
Diseases of the Heart
Oxford University Press, 1908

"It is hard to see . . . how a man will be more of a physician by having thought about the ideal of the good, for the

This article is part of a series of articles celebrating the 40th Anniversary of the American College of Cardiology. The series attempts to set the stage for the future by describing current state of the art management of selected major cardiovascular problems and the basic knowledge that will provide directions for advances in diagnosis and therapy.

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0735-1097/89/$3.50

physician does not appear to investigate health in this way, but instead studies the health of man; or rather, of a particular man. For he cares for each man as an individual."

Aristotle
The Nicomachean Ethics
Translated by P. B. Katz

Introduction

The 40th anniversary of the American College of Cardiology comes at a time of dramatic change in the management of congestive heart failure. Rapid developments in our understanding of normal cardiac function and the pathogenesis of this common condition illustrate the growing impact of the basic sciences on clinical practice, and the way that concepts developed in the research laboratory come to influence strategies for the care of the patient (1). This article reviews current understanding of the regulation of cardiac function, and the way that clinical applications of these basic principles are changing the treatment of patients with congestive heart failure.

What is Heart Failure?

A simple definition of heart failure is not possible as this condition arises from a variety of pathophysiologic processes; furthermore, the clinical manifestations of heart failure may differ considerably, even among patients in whom the condition arises from a single process like mitral stenosis (2). Most definitions focus on the clinical presentation of the patient with heart failure and especially on the syndromes that appear when the failing heart becomes unable to meet the hemodynamic demands of the body. I believe, however, that this hemodynamic approach to the definition of heart failure perpetuates an outdated tradition that, by emphasizing the circulatory impairment, inadequately recognizes important cellular changes in the hypertrophied and failing heart. For these myocardial cellular abnormalities, rather than the disordered circulation, are largely responsible for the poor prognosis in these patients, about 50% of whom die within 5 years after an initial diagnosis of heart failure (3). Definitions of heart failure that focus on disorders of the circulation, which in fact represent not the cause but the consequences of an impaired ability of the heart to meet the demands of the body, are therefore incomplete. It can even be argued that to define heart failure in terms of abnormal hemodynamics inappropriately diverts attention from important cellular abnormalities that develop in the hypertrophied heart. Such definitions, by not recognizing a *cardiomyopathy of overload* as one of the major causes of clinical deterioration and death, can misdirect therapeutic strategies for this common and deadly condition.

MacKenzie's definition of heart failure, which is reproduced at the beginning of this article, highlights the interplay between the heart and circulation. MacKenzie clearly understood the primary role of the myocardial abnormalities in heart failure when he wrote:

> "The more I study the symptoms of heart failure, and the more I reflect on the part played by the heart muscle, the more convinced I am that the explanation of heart failure can be summed up in the general statement that heart failure is due to the exhaustion of the reserve force of the heart muscle . . ." (4).

Although the "reserve force of the heart muscle" could not be understood in terms of the science of 1908, research over the past 81 years has clarified the mechanisms that control the contractile processes in the heart. Today, this knowledge provides the foundation for new therapeutic strategies that, when individualized to treat specific abnormalities present in each patient with heart failure, both relieve symptoms and improve prognosis.

Table 1. Three Mechanisms That Regulate the Work of the Heart

Regulation by changing end-diastolic fiber length (Starling's law of the heart).
Beat to beat responses to altered hemodynamics; adjustment of cardiac output to changing preload and afterload, and equalization of the outputs of the two ventricles.
Regulation by biochemical changes within the myocardial cell (excitation-concentration coupling and myocardial contractility).
Short-term responses of the heart to physiologic and pharmacologic interventions; e.g., neurotransmitters and cardiac drugs.
Regulation by altered gene expression (molecular biology).
Long-term adaptation of myocardial cells to the functional heterogeneity of the heart, and to chronic changes in cardiac loading, endocrinopathies and aging.

Three Mechanisms That Regulate the Work of the Heart

Current approaches to the therapy of heart failure are based on the new understanding that the work of the heart is regulated by at least three fundamentally different mechanisms (Table 1). Although each plays a unique role in adjusting the performance of the heart to the needs of the body, it is their interplay that defines cardiac and circulatory regulation in health and disease (5).

Forty years ago, only the role of changing *end-diastolic fiber length* (Starling's law of the heart) was understood; this mechanism operates at the organ level to adjust the output of the heart to changing preload and afterload on a beat to beat basis. Changes in *myocardial contractility*, which regulate cardiac performance over a slower time course largely by altering the calcium fluxes involved in excitation-contraction coupling, came to be understood over the past 25 years. This biochemical mechanism allows individual myocardial cells to respond to humoral stimuli, such as the sympathetic

Table 2. Changing Strategies in the Management of Congestive Heart Failure

Phase I (1948 to 1968): Digitalis and Diuretics	
Cardiac glycosides	Increase inotropy; reduce dromotropy in atrial fibrillation
Diuretics	Reduce preload
Phase II (1968 to 1978): Vasodilators	
Alpha-adrenergic blockers	Reduce preload and afterload
Nitrates	Reduce preload
Arteriolar dilators	Reduce afterload
Calcium channel blockers	Reduce afterload
Phase III (1978 to 1988): Inotropic stimulation	
Beta–adrenergic agonists	Increase inotropy and lusitropy
Calcium sensitizing agents	Increase inotropy
Phosphodiesterase inhibitors	Increase inotropy and lusitropy
Phase IV (1988–): Preserve the failing heart	
Converting enzyme inhibitors	Reduce preload and afterload Reduce inotropic stimulation
Beta-adrenergic blockers	Reduce inotropy
Phase V (?): Correct the myocardial abnormality	
??	Modify synthesis of abnormal gene products

Data are approximations.

neurotransmitters released during exercise. Regulation by *variable gene expression*, the third of these mechanisms, brings about changes in myocardial protein composition that alter cardiac function over an even slower time course; for example, in the response to chronically altered cardiovascular function as occurs in endocrinopathies, aging and chronic hemodynamic overloading (6–8). Regulation by variable gene expression also makes possible a remarkable cellular and molecular heterogeneity that underlies the essential functional homogeneity of the heart as an organ (5,9).

The evolution of our understanding of the regulatory mechanisms listed in Table 1 has contributed to the changing management of congestive heart failure summarized in Table 2. Starling's law of the heart and alterations in myocardial contractility, which until recently dominated thinking in cardiology, had initially determined strategy for managing patients with congestive heart failure. However, it is now apparent that optimal therapy for these patients must also be based on knowledge of the altered composition and behavior of the overloaded cells of the failing heart. Thus, to treat the patient with congestive heart failure, the physician must understand the interplay between all three of the regulatory mechanisms that determine the state of the circulation, the heart and the individual cells of the myocardium.

Strategies for the Management of Congestive Heart Failure. Phase I: Digitalis and Diuretics

Forty years ago, treatment of heart failure focused largely on two groups of drugs, the cardiac glycosides and mercurial diuretics. The former had been in use for >150 years, since Withering (10) had identified the foxglove as the active ingredient in a secret family recipe used to treat dropsy. Calomel (mercurous chloride), like digitalis, had been recognized to induce diuresis in patients with dropsy since the latter half of the 18th century; however, the toxicity and unpredictable effects of this inorganic mercurial precluded its routine use. It was not until 1920 that the diuretic effect of the organic mercurials was discovered accidentally in a patient who was receiving one of these compounds for the treatment of syphilitic aortitis (11). Supplemented by the weaker diuretic actions of the xanthines, the organic mercurials had joined digitalis as standard therapy for heart failure when the American College of Cardiology was founded in 1949.

Strategies for the Management of Congestive Heart Failure. Phase II: Vasodilators

Heart Failure as a Hemodynamic Abnormality

It is possible to trace the beginnings of the second phase in the evolution of our strategy for the management of heart failure to the introduction of cardiac catheterization into clinical medicine shortly after World War II. This Nobel prize-winning advance made it possible to evaluate heart failure in terms of basic hemodynamic principles and overall cardiac energetics, topics once viewed as only of theoretical interest. Measurements of cardiac output and pressures in the cardiac catheterization laboratory, and the development of flow-directed catheters in the coronary care unit, made it possible to characterize hemodynamic abnormalities in pa-

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tients with both chronic and acute heart failure. This approach provided the basis for the second phase in the evolving strategy for managing heart failure (Table 2) when measurements of peripheral resistance in patients with heart failure made it possible to understand how vasoconstriction, long known to be compensatory in acute heart failure (12), contributed to the clinical disability in patients with chronic heart failure (13). Recognition of the detrimental effects of vasoconstriction in turn provided a foundation for later demonstrations that afterload reduction could relieve symptoms (14) and prolong life (15) in patients with heart failure. Today, of course, vasodilator therapy has joined digitalis and diuretics as standard therapy for this condition.

Strategies for the Management of Congestive Heart Failure. Phase III: Inotropic Stimulation

Heart Failure as an Abnormality of Myocardial Cell Biochemistry: Depressed Contractility in the Failing Heart

At the same time that improved understanding of the interplay between the heart and circulation refined strategies for the management of heart failure through manipulation of the peripheral vasculature, it was becoming apparent that the cardiac abnormality in patients with heart failure involved more than abnormal cardiac metabolism (16–18) and the descending limb of the Starling curve (19). Yet as recently as the mid 1960s, the importance, and indeed the existence, of cardiac muscle abnormalities in the patient with heart failure had not been established, and myocardial contractility had not been shown to be depressed in these patients. Thus, in summarizing the deliberations of a distinguished group of cardiologists and cardiovascular physiologists who examined this question in 1964, I was forced to write: ". . . the basic question: 'Is the failure of chronically overloaded hearts the result of abnormalities within the cardiac fiber?' remains unanswered . . ." (20). This question was answered only when myocardial contractility (MacKenzie's "reserve force"), came to be understood in biochemical and biophysical terms (Table 1). Characterization of the state of the myocardium in patients with congestive heart failure became possible when the work of the heart was recognized to be regulated by changes in *myocardial cell biochemistry*, which were expressed clinically as abnormalities in *myocardial contractility*.

Our present understanding of the role of depressed myocardial contractility in the pathogenesis of heart failure is based on two lines of research, both of which were stimulated by the observation that factors other than end-diastolic fiber length determined the performance of the heart (5,21). Recognition that changing properties of individual myocardial cells played a major role in controlling the work of the heart (Table 2) stimulated efforts to characterize the mechanical behavior of the heart in terms of skeletal muscle mechanics (22,23). At the same time, rapid progress in our understanding of the biochemical and biophysical processes that regulate myocardial contractility made clear the central role of Ca^{2+} in cardiac excitation-contraction coupling (24). Application of this new understanding to evaluate myocardial function in humans led to the demonstration that myocardial contractility was, in fact, depressed in patients with heart failure (25).

The Search for the Ideal Inotropic Agent

A seemingly obvious corollary to the depressed myocardial contractility in patients with heart failure, which until recently dominated strategy for management of this syndrome, was that the condition of these patients would be improved by increasing contractility in the failing heart. The conclusion that more powerful inotropic stimulation would be beneficial to these patients gained support from clinical experience in the coronary care unit, where temporary inotropic support of the failing left ventricle was of clear value in treating the acute heart failure that followed massive myocardial infarction. The view that survival could be similarly improved by increasing myocardial contractility in chronic congestive heart failure stimulated a search for improved means to increase contractility in these patients.

Cardiac glycosides. Forty years ago, the cardiac glycosides were the only useful positive inotropic agent for the treatment of heart failure. I suspect, however, that the benefit of these agents was due, in large part, to their ability to slow ventricular rate in atrial fibrillation. Such a view had been expressed by two of the giants of British cardiology. Sir James MacKenzie wrote in 1918:

> "In searching the records in literature for the evidence of the good effects of digitalis, I feel fairly certain that it is in patients with auricular fibrillation, particularly when it is subsequent to rheumatic fever, that the extraordinarily good results have been obtained. If one reads carefully the records given by Withering in the first valuable account of digitalis in 1785, though he used it as a diuretic, yet he noted its good effects in heart cases; and several of his successful cases had undoubtedly auricular fibrillation" (26).

Twenty years later, Sir Thomas Lewis wrote: "It is to their striking effect in cases of auricular fibrillation that drugs of the digitalis group almost conclusively owe their well-founded reputation" (27). Even in the 1940s, rheumatic heart disease was the leading cause of heart failure, affecting about 2% of the population (28), and atrial fibrillation was found in about 40% of patients with mitral stenosis (29).

Regardless of the basis for their wide acceptance, the cardiac glycosides were given as a matter of course to

virtually every patient who appeared to be suffering from congestive heart failure. However, the low therapeutic/toxic ratio of the cardiac glycosides had, for years, stimulated unsuccessful efforts to identify a safer drug of this class. This search ended only recently when it was realized that the therapeutic and toxic effects of the cardiac glycosides both arose from the same molecular interaction of these drugs with the cardiac cell, which by inhibiting the sodium pump (30), increases intracellular sodium concentration and so promotes calcium entry by Na/Ca exchange (31).

Early inotropic agents. Although the benefit derived from the positive inotropic actions of the catecholamines in the short-term management of patients with acute myocardial infarction suggested their possible usefulness in chronic congestive heart failure, most inotropic drugs available 40 years ago were poorly suited for long-term administration. The sympathomimetic amines of that time had chronotropic and arrhythmogenic side effects that precluded their routine use in the management of chronic congestive heart failure, whereas phosphodiesterase inhibitors like aminophylline were short-acting and sometimes caused arrhythmia and sudden death.

Paired pulse stimulation. The inotropic effect of postextrasystolic potentiation enjoyed a brief moment in the spotlight of clinical cardiology over 20 years ago (32). This now almost forgotten inotropic therapy attempted to use the marked potentiation of the contraction after a premature systole, a manifestation of the positive (Bowditch) staircase, to treat heart failure. Although paired pulse stimulation was once viewed as having clinical potential in the management of patients with heart failure, the risk of inducing arrhythmias and interference with ventricular filling by the premature systoles was quickly recognized and this hazardous approach to therapy was abandoned.

New inotropic agents. The search for new inotropic drugs was facilitated by rapid advances in our understanding of the ability of cyclic adenosine monophosphate (AMP), the second messenger that mediates the cellular effects of sympathomimetic amines, to modify the Ca^{2+} fluxes responsible for cardiac excitation-contraction coupling. It now appears that, with the notable exception of the cardiac glycosides, most inotropic agents that have been examined clinically act by increasing the rate of cyclic AMP production or decreasing the rate of breakdown of this second messenger (33). Whereas the bipyridines, introduced a decade ago as "novel" inotropic drugs, are now generally accepted to be phosphodiesterase inhibitors, another class of new agents, the imidazopyridines, increase the Ca^{2+} sensitivity of the contractile proteins (34). Clinical applications of drugs that modify various ion channels in the cardiac sarcolemma are still to be found; examples are agents that prolong sodium channel opening, and so promote calcium entry through exchange of the increased cellular Na^+ with extracellular Ca^{2+} by way of Na/Ca exchange (35). Other inotropic drugs delay the closing of the potassium channels that cause membrane repolarization; the resulting increase in action potential duration prolongs calcium channel opening and so increases cellular Ca^{2+}. Although these mechanisms are of promise in the development of truly novel inotropic drugs, new knowledge of the pathophysiology of heart failure is bringing this phase in the management of congestive heart failure to a close.

Limitations on the Use of Inotropic Agents for the Management of Congestive Heart Failure

Major conceptual advances in our understanding of the cardiac abnormalities in patients with congestive heart failure are now shifting therapeutic strategies away from efforts to increase contractility. This redirection of the goals of therapy is due in part to the recognition of the role of relaxation abnormalities in these patients and to the realization that relaxation is especially sensitive to an imbalance between energy production and energy utilization in the myocardium.

Importance of relaxation (lusitropic) abnormalities. Emphasis on inotropic abnormalities during the "phase of inotropic stimulation" (Table 2) reflected the widely held view that heart failure was due entirely, or at least largely, to impaired ability of the heart to contract. This focus on systolic abnormalities was, in no small measure, a reflection of the utilization of intraventricular pressure measurements as the reference standard for evaluating ventricular function. As the indexes most easily derived from pressure curves occur during the isovolumic phase of systole, such estimates of myocardial contractility as positive first derivative of left ventricular pressure (+dP/dt), V_{max}, and V_{CE} once dominated the assessment of cardiac dysfunction in patients with heart failure. Because of difficulties in evaluating relaxation by the use of pressure-derived indexes based on catheterization data, it was not until the introduction of noninvasive methods for the study of ventricular wall motion (echocardiography) and volume changes (nuclear cardiology) that simple and accurate evaluations of diastolic function became feasible in the failing human ventricle (36). Over the past decade, these new clinical methods revealed that relaxation abnormalities played a much greater role in the pathogenesis of heart failure than had previously been suspected (37).

Energy is required for the heart to relax. Recognition of the importance of relaxation abnormalities in the pathogenesis of congestive heart failure highlighted the clinical significance of the fact that relaxation, like contraction, is an energy-requiring process (38). This raised the possibility that the lusitropic abnormalities commonly encountered in these patients might be due to a lack of energy in the overloaded myocardium, and so added to earlier concerns (39) that inotropic stimulation, by increasing energy expenditure in

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the failing heart, might represent an inappropriate strategy for routine therapy of congestive heart failure (40,41).

Is the failing heart an energy-starved heart? In most patients with heart failure, whether due to hemodynamic overloading, loss of functional myocardial tissue or a valve abnormality, the work of the active myocardial cells, and so their expenditure of energy, are increased on a long-term basis. However, there is abundant evidence, albeit mostly indirect, that the cells of the hypertrophied and failing heart are unable to generate sufficient energy to provide for this increased rate of energy expenditure; as a result, the failing heart is likely to be in an energy-starved state (42).

A number of changes that occur in the failing heart can impair the ability of the hypertrophied myocardial cells to meet their increased energy needs. Intercapillary distance is increased (43) and there is a decreased number of transverse capillary profiles per square millimeter (44); both would increase the distance required for the diffusion of substrates, notably oxygen, to the cells of the hypertrophied heart. A resulting predisposition to a state of energy deficiency would be especially severe in the relatively underperfused subendocardial regions of the hypertrophied ventricle (45).

Changes in the composition of the cells in the chronically overloaded myocardium represent another possible cause for an energy-starved state in the failing heart. Several experimental studies (44,46,47) have shown that the fraction of cell volume occupied by myofibrils in the hypertrophied heart is increased, whereas mitochondrial mass decreases; changes that could exacerbate an energy deficit by increasing the number of adenosine triphosphate (ATP)-consuming myofibrils that must be supported by each ATP-generating mitochondrion.

Myocardial high energy phosphate content has been found to be decreased in the pressure-overloaded left (48) and right (49) ventricles in animal models of heart failure. Cardiac biopsies in patients with congestive heart failure have also shown that reduced content of high energy phosphate compounds (50) correlates with the extent of impairment of both contraction and relaxation (51). These data are consistent with the view that a chronic myocardial energy deficit contributes to the deterioration in patients with chronic congestive heart failure.

Strategies for the Management of Congestive Heart Failure. Phase IV: Preserve the Failing Heart

Much like the once prevalent "senescence" theory of atherosclerosis as an inevitable consequence of the aging process (52), the progressive deterioration in patients with congestive heart failure was, until a few years ago, thought to be unavoidable and untreatable. This fatalistic view was heightened by the fact that heart failure often results from clinical conditions, such as some of the cardiomyopathies, that are themselves progressive. As recently as the mid 1980s, therapy of severe congestive heart failure was believed to have little likelihood of improving the poor prognosis in these patients (53).

This hopeless view of congestive heart failure was dramatically reversed by recent demonstrations that medical therapy could, in fact, significantly prolong life (15,54) and slow cardiac deterioration (55) in these patients. This realization has stimulated a new emphasis on efforts to preserve the failing heart and added significance to studies of the molecular biology of the overloaded myocardium.

Spontaneous Deterioration of the Hypertrophied Heart

Almost a century ago, Osler (56) recognized that the clinical state in patients with a hemodynamically overloaded heart follows a predictable course. The first response to a lesion like acute aortic regurgitation is a period of "development," during which the myocardium hypertrophies to meet the increased load. This leads into a stage of "compensation," in which acute heart failure caused by the increased load is alleviated as hypertrophy distributes the increased load among a larger number of cardiac fibers. Osler recognized, however, that the hypertrophied heart tends to undergo spontaneous, progressive deterioration in a final stage of "broken compensation."

The cardiomyopathy of overload. The modern era of understanding the causes of deterioration of the overloaded heart began with the monumental work of Meerson (57), who found that experimental aortic coarctation causes the myocardium to undergo a sequence of structural and biochemical changes that lead to fibrosis and cell death (Table 3). Hypertrophy, which begins during the initial phase in this sequence (analogous to Osler's "development"), represents a beneficial response as the increased mass of heart muscle distributes the overload among a greater number of sarcomeres (analogous to Osler's "compensation"). However, this response carries with it a heavy price; much like Faust's bargain with the devil, a brief period of pleasure is followed by an eternity of pain! This occurs because the cells of the hypertrophied heart are not normal and, in the face of sustained overloading, deteriorate and die (analogous to Osler's "broken compensation"), thereby initiating a vicious cycle by further increasing the load on the surviving cells (Fig. 1). The response of the heart in patients with congestive heart failure therefore resembles that of the circulation described by Harris (12), where mechanisms like vasoconstriction and sodium retention are compensatory for the short term, but come to have deleterious long-term effects. It is clear that, as stated over 20 years ago: "the failing heart is not simply an enlarged version of the normal heart" (58). On the contrary, the cells of the hypertrophied heart undergo a progressive deterioration that can be viewed

Table 3. Three Stages in the Response to a Sudden Hemodynamic Overload

Stage 1 (days): Transient breakdown
Circulatory: Acute heart failure; pulmonary congestion, low output
Cardiac: Acute left ventricular dilation, early hypertrophy
Myocardial: Increased content of mitochondria relative to myofibrils
Stage 2 (weeks): Stable hyperfunction
Circulatory: Decreased pulmonary congestion and improved cardiac output
Cardiac: Established hypertrophy
Myocardial: Increased content of myofibrils relative to mitochondria
Stage 3 (months): Exhaustion and progressive cardiosclerosis
Circulatory: Progressive left ventricular failure
Cardiac: Further hypertrophy with progressive fibrosis
Myocardial: Cell death

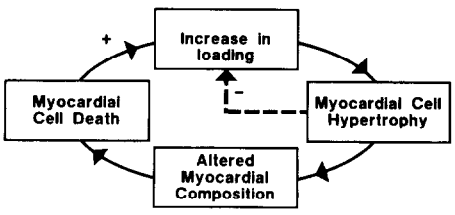
This table is based on experimental studies of the response of the heart to aortic constriction described by Meerson (57).

as a "cardiomyopathy of overload," which may become a major determinant of the downhill course in patients with this condition.

Possible role for energy starvation. A clue to the mechanisms responsible for the progressive deterioration of the overloaded myocardium is found in the "stone heart syndrome." This form of ischemic contracture was described by Cooley et al. (59) in patients with severe left ventricular hypertrophy who underwent open heart surgery with inadequate cardioplegia. This syndrome, which appears to result from high energy phosphate depletion that occurs when the severely overloaded heart become ischemic (60), may represent a model for the slower myocardial cell deterioration seen when patients with chronic congestive heart failure are treated medically.

A word of caution is in order, however. If the past is any guide to the future (1,5,21), the final answer to the important question of what causes the progressive deterioration in the overloaded heart is likely to be far more complex than can be imagined today. For example, it is by no means impossible that accelerated senescence accompanies the hypertrophy that develops in the cells of the overloaded heart.

Figure 1. By increasing the number of contractile units, and so reducing the loading on each sarcomere of the overloaded heart (−), hypertrophy is beneficial. However, hypertrophy also initiates myocardial changes that lead ultimately to cell death. As a result, hypertrophy perpetuates a vicious cycle that, by reducing the number of contractile units, increases the load on each of the surviving cells (+).



Morphologic changes in the hypertrophied heart. Complex morphologic abnormalities in hypertrophied and failing hearts have long been recognized. Using light microscopy, Linzbach (61) observed that the myocardial cells are uniformly and moderately enlarged in the mildly hypertrophied heart ("concentric hypertrophy"), whereas he attributed thinning of the wall of the heart in more severe heart failure ("eccentric hypertrophy") to weakening of connective tissue and destruction of myofibers. It is now apparent that changes in the extracellular matrix of the hypertrophied heart reflect very complex processes; for example, fibrosis involves not only changes in the amount of collagen, but also the appearance of different types of collagen during the different phases of the response to overload (62). Evidence that chronic overloading of the heart leads to changes in cardiac composition (44,46,47) and alterations in the number of beta-adrenergic receptors (63) provides further examples of important changes in the composition of the hypertrophied and failing heart.

Heart Failure as an Abnormality of Gene Expression in the Myocardium

Molecular changes now recognized to occur in the individual proteins of the hypertrophied and failing heart have functional consequences that can be both compensatory and deleterious in the patient with congestive heart failure. Alpert and Gordon (64) first suggested such molecular changes when they reported that cardiac myosin adenosine triphosphate (ATPase) activity is depressed in congestive heart failure. Subsequent demonstrations that cardiac myosin ATPase activity changes not only in response to chronic overload, but also in aging and the endocrinopathies (65), suggested that altered protein structure represents a "tonic" mechanism (6) by which myocardial function becomes adapted to long-term circulatory changes (Table 1). These early concepts have recently been incorporated into the

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fast-moving fields of "molecular biology," which are demonstrating a hitherto unimagined degree of molecular heterogeneity in the proteins of the myocardium (9).

Variability of gene expression in the heart. Growing knowledge of the mechanisms responsible for the remarkable variability of gene expression in the heart has defined a key role for changes in the cardiac proteins in determining the myocardial response in patients with heart failure. Although this field is still in its infancy, characterization of cardiac myosin, the major protein of the thick filament that is readily isolated in pure form and in large amounts from heart muscle, illustrates a number of important functional and biochemical features of these changes in gene expression (66–68). These focus on the myosin "heavy chains," which determine the rate of energy liberation by myosin both in vitro (ATPase activity) and in vivo (muscle shortening velocity).

The myosin heavy chains, which are encoded by several gene families, are expressed differently among different muscles and at different times in a single muscle during ontogeny (67). In the adult heart, chronic hemodynamic overloading and heart failure are among the most important causes of altered cardiac myosin gene expression (66,69–75). This is readily apparent in the rat ventricle, which can express several myosin heavy chain isoforms; the V_1 (alpha) myosin heavy chain determines a high myosin ATPase activity and rapid shortening velocity, whereas the V_3 (beta) myosin heavy chain determines low myosin ATPase activity and slow shortening velocity. In the overloaded, hypertrophied myocardium, the preferential synthesis of the messenger ribonucleic acid that encodes the low ATPase V_3 heavy chain (74) leads to the replacement of fast myosin with slow myosin, which decreases the rate of cross-bridge cycling and so reduces myocardial contractility. However, at the same time that this alteration in gene expression has a negative inotropic effect, mechanical efficiency is increased (8,39). Thus, one result of the changing expression of different myosin heavy chain genes in hypertrophy is an energy-sparing effect that facilitates the adaptation of the heart to the chronically increased hemodynamic load. Although the human ventricle is now recognized to contain only one myosin heavy chain isoform, a similar change in myosin gene expression has been observed in overloaded human atria, where a decreased proportion of fast (alpha) atrial myosin heavy chain parallels the extent of left atrial enlargement (76).

Expression of different protein isoforms in the hypertrophied heart has also been reported for two proteins of the thin filament; actin (77,78) and tropomyosin (78). This response represents more than a simple "up-regulation" of sarcomere synthesis, as is apparent from evidence that expression of altered myosin and actin isoforms follows different time courses (77,78).

Isoform changes in the hypertrophied heart have also been reported for lactate dehydrogenase (79), creatine kinase (80,81) and the sarcolemmal sodium pump (82). That this list is incomplete is evidenced by major functional changes in the failing heart that have not yet been explained at a molecular level. Among the latter is the severely impaired relaxation seen when heart muscle from patients with dilated or hypertrophic cardiomyopathy is studied in vitro (83). Although this lusitropic abnormality may be due in part to a deficit in chemical energy, the mechanism appears to be more complex and may involve increased sensitivity of the energy-dependent reactions that relax the heart to as yet poorly understood energetic abnormalities in the hypertrophied myocardium (84).

Therapeutic implications of excessive energy demands by the hypertrophied heart. Demonstration that changes in the synthesis of specific myocardial proteins reduce contractility in the hypertrophied heart raises fascinating questions as to whether these changes are compensatory or deleterious. I believe that they are both (39). Insofar as the changes in myosin heavy chain isoforms synthesized by the overloaded heart reduce myocardial contractility, the alterations in gene expression are detrimental to pumping by the failing heart. This view has, in the past, provided a rationale for efforts to increase myocardial contractility in patients with heart failure. At the same time, however, the important energy-sparing effect of depressed contractility could preserve myocardial cell viability in an energy-starved heart and so, like afterload reduction, might prolong survival in patients with congestive heart failure.

A logical corollary to the interpretation that depression of contractility in the overloaded heart has a potentially beneficial energy-sparing effect is that negative inotropic agents could be of value in preserving cell viability in the chronically overloaded heart (39). Such an interpretation is supported by the ability of vasodilators to prolong survival and preserve myocardial function in patients with congestive heart failure (15,54,55), a beneficial effect that may be due, at least in part, to a reduced rate of energy utilization by the overloaded cells of the failing heart (42). The ability of negative inotropic drugs to produce a similar energy-sparing effect may explain the results of several clinical trials (85–90) that indicate that beta-adrenergic blocker therapy can prolong survival and slow deterioration in patients with heart failure. Although these observations in no way deny the hazards of negative inotropic therapy in heart failure, especially when it is acute as in cardiogenic shock, they offer hope that means are at hand to alter further the bleak prognosis in patients with chronic congestive heart failure.

Strategies for the Management of Congestive Heart Failure. Phase V: Correct the Myocardial Abnormality

Should efforts be made to modify the evolution of hypertrophy in the failing heart? We have seen how the remarkable plasticity in cellular composition of the myocardium gives rise to important functional changes in the hypertro-

phied, failing heart. By providing more sarcomeres to aid the heart in meeting the overload caused by a variety of disease processes, hypertrophy is initially compensatory; however, because hypertrophy also initiates processes that may lead to myocardial cell death, this response can lead to a cardiomyopathy of overload that becomes part of the pathologic process itself (Fig. 1). Although attempts to modify deterimental changes in gene expression in the patient with congestive heart failure are not yet feasible, the likely existence of a cardiomyopathy of overload should stimulate efforts to formulate new strategies to modify gene expression in the failing heart.

Conclusions

As it is essential to understand the past before attempting to predict the future, this article has focused largely on the history of strategies for the therapy of congestive heart failure. Three important points can be drawn from this historic survey. *The first, apparent when Table 2 is examined in light of Table 1, is that new clinical strategies, although often initiated by thoughtful and careful clinical observation, become established when they find support in concepts derived from basic research.* I do not mean to imply that innovations in clinical practice depend on basic research; more often, it is the other way around in that novel observations in patients frequently direct basic research to important clinical problems. In fact, new ideas in medicine find clinical application most rapidly when basic and clinical science advance together.

The second point of this review is that the pace of scientific advance is accelerating (Table 2). It is no exaggeration that we have learned more of value about the therapy of heart failure in the past 10 years than had been learned previously since the dawn of time (91).

Finally, the history of science teaches us that important advances come from unexpected directions. This caveat notwithstanding, it seems safe to predict that better understanding of regulation of gene expression, coupled with new knowledge about the biochemistry of the hypertrophied and failing heart, will provide means by which myocardial composition can be altered so as to benefit the patient with congestive heart failure. Such a capability could allow the fifth of the strategies set forth in Table 2 to be achieved; but how to restore normal structure and function in the myocardium of the patient with congestive heart failure is, of course, a question for future research.

I thank my colleagues and the fellows, residents and students at the University of Connecticut, with whom this topic has been elucidated through ongoing discussion and debate. I thank especially Frank C. Messineo, MD and W. David Hager, MD for their careful reading of this manuscript and help in clarifying many salient points of this review.

References

1. Katz AM. Role of the basic sciences in the practice of cardiology. J Mol Cell Cardiol 1987;19:3–17.
2. Wood P. An appreciation of mitral stenosis. Br Med J 1954;1:1051–63, 1113–24.
3. Kannel WB. Epidemiology and prevention of congestive heart failure: Framingham Study insights. Eur Heart J 1987;8(suppl F):23–39.
4. MacKenzie J. Diseases of the Heart. Oxford: Oxford University Press, 1908.
5. Katz AM. Molecular biology in cardiology, a paradigmatic shift. J Mol Cell Cardiol 1988;20:355–66.
6. Katz AM. Tonic and phasic mechanisms in the regulation of myocardial contractility. Basic Res Cardiol 1976;71:447–55.
7. Bugaisky L, Zak R. Biological mechanisms of hypertrophy. In: Fozzard H, Haber E, Katz A, Jennings R, Morgan HE, eds. The Heart and Cardiovascular System. New York: Raven, 1986:1491–506.
8. Hamrell BB, Alpert NA. Cellular basis of the mechanical properties of hypertrophied myocardium. In Ref. 7:1507–24.
9. Katz AM, Katz PB. Homogeneity out of heterogeneity. Circulation (in press).
10. Withering W. An Account of the Foxglove and Some of its Medical Uses: With Practical Remarks on Dropsy and other Diseases. London: CGJ Robinson, 1785.
11. Saxl P, Heilig R. Übar die diuretische Wirkung von Novasurol und andern Quecksilberinjecktionen. Wein Klin Wochenschr 1920;33:943.
12. Harris P. Evolution and the cardiac patient. Cardiovasc Res 1983;17: 313–9, 373–8, 437–45.
13. Ross J Jr. Afterload mismatch and preload reserve: a conceptual framework for the analysis of ventricular function. Prog Cardiovasc Dis 1976; 18:255–64.
14. Cohn J, Franciosa JA. Vasodilator therapy of cardiac failure. N Engl J Med 1977;297:27–31, 254–57.
15. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration cooperative study (V-HeFT). N Engl J Med 1986;314: 1547–52.
16. Katz LN. Analysis of the several factors regulating the performance of the heart. Physiol Rev 1955;35:91–106.
17. Olson RE. Myocardial metabolism in congestive heart failure. J Chronic Dis 1959;9:442–64.
18. Bing RJ. Cardiac metabolism. Physiol Rev 1965;45:171–213.
19. Katz AM. The descending limb of the Starling curve and the failing heart. Circulation 1965;32:871–5.
20. Katz AM. Fundamental mechanisms in myocardial failure. In: The Heart and Circulation. Second National Conference on Cardiovascular Diseases. Research. Washington, DC: FASEB J 1965;1:533–7.
21. Katz AM. Regulation of myocardial contractility, 1958–1983: an odyssey. J Am Coll Cardiol 1983;1:42–51.
22. Abbott BC, Mommaerts WHFM. A study of inotropic mechanisms in the papillary muscle preparation. J Gen Physiol 1959;42:533–51.
23. Sonnenblick EH. Implications of muscle mechanics in the heart. Fed Proc 1962;21:975–90.
24. Katz AM. Regulation of cardiac muscle contractility. J Gen Physiol 1967;50:185–96.
25. Braunwald E, Ross J Jr, Sonnenblick EH. Mechanisms of Contraction of the Normal and Failing Heart. 2nd ed. Boston: Little, Brown, 1975.
26. MacKenzie J. Diseases of the Heart. 3rd ed. Oxford: Oxford University Press, 1918.
27. Lewis T. Diseases of the Heart. New York: Macmillan, 1933.
28. Wilson MG. Rheumatic Fever. New York: The Commonwealth Fund, 1940.

29. Wood P. Diseases of the Heart and Circulation. 2nd ed. Philadelphia: JB Lippincott, 1956.

30. Katz AM. Effects of digitalis on cell biochemistry: sodium pump inhibition. J Am Coll Cardiol 1985;5:16A–21A.

31. Lee CO, Abete P, Pecker M, Sonn JK, Vasalle M. Strophanthidin inotropy: role of intracellular sodium ion activity and sodium-calcium exchange. J Mol Cell Cardiol 1985;17:1043–53.

32. Cranefield P, ed. Conference on paired pulse stimulation and postextrasystolic potentiation in the heart. Bull NY Acad Med 1965;41:417–748.

33. Scholz H. Inotropic drugs and their mechanisms of action. J Am Coll Cardiol 1984;4:289–97.

34. Solaro JR, Ruegg JC. Stimulation of Ca^{++} binding and ATPase activity of dog cardiac myofibrils by AR-L115BS. Circ Res 1968;51:290–4.

35. Luellman H, Peters J, Ravens U. Pharmacological approaches to influence cardiac inotropism. Pharmacol Ther 1983;21:229–45.

36. Smith VE, Katz AM, Weisfeldt ML. Relaxation and diastolic properties of the heart. In: Ref. 7:803–18.

37. Grossman W, Lorell BH. Diastolic Relaxation of the Heart. Boston: Martinus Nijhoff, 1988.

38. Katz AM. Potential deleterious effects of inotropic agents in the therapy of chronic heart failure. Circulation 1986;73(suppl III):III-184–8.

39. Katz AM. Biochemical "defect" in the hypertrophied and failing heart: deleterious or compensatory? Circulation 1973;47:1076–9.

40. Katz AM. A new inotropic drug: its promise and a caution. N Engl J Med 1978;299:1409–10.

41. LeJemtel TH, Sonnenblick EH. Should the failing heart be stimulated? N Engl J Med 1984;310:1384–5.

42. Katz AM. The myocardium in congestive heart failure. Am J Cardiol 1989;63:12A–6A.

43. Roberts JT, Wearn JT. Quantitative changes in the capillary-muscle relationship in human hearts during normal growth and hypertrophy. Am Heart J 1941;21:617–23.

44. Anversa P, Olivetti G, Melissari M, Loud AV. Stereological measurement of cellular and subcellular hypertrophy and hyperplasia in the papillary muscle of adult rat. J Mol Cell Cardiol 1980;12:781–95.

45. Hoffman JEI. Transmural myocardial perfusion. Prog Cardiovasc Dis 1987;29:429–64.

46. Page E, McCalister LP. Quantitative electron microscopic description of heart muscle cells: application to normal, hypertrophied and thyroxin-stimulated hearts. Am J Cardiol 1973;31:172–81.

47. Rabinowitz M. Protein synthesis and turnover in normal and hypertrophied heart. Am J Cardiol 1973;31:202–10.

48. Furchgott RF, Lee KS. High energy phosphates and the force of contraction of cardiac muscle. Circulation 1961;24:416–28.

49. Pool PE, Spann JF, Buccino RA, Sonnenblick EH, Braunwald E. Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure. Circ Res 1967;1:365–73.

50. Swain JL, Sabina RL, Peyton RB, et al. Derangements in myocardial purine and pyrimidine nucleotide metabolism in patients with coronary artery disease and left ventricular hypertrophy. Proc Natl Acad Sci USA 1982;79:655–9.

51. Bashore TM, Magorien DJ, Letterio J, Shaffer P, Unverferth DV. Histologic and biochemical correlates of left ventricular chamber dynamics in man. J Am Coll Cardiol 1987;9:734–42.

52. Katz LN. Experimental atherosclerosis. Circulation 1952;5:101–14.

53. Braunwald E. Newer positive inotropic agents: concluding comments. Circulation 1986;73(suppl III):III-237.

54. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure: results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). N Engl J Med 1987;316:1429–35.

55. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E. Effect of captopril on progressive ventricular dilatation after anterior myocardial infarction. N Engl J Med 1988;319:80–6.

56. Osler W. The Principles and Practice of Medicine. D Appleton, 1892:634.

57. Meerson FZ. On the mechanism of compensatory hyperfunction and insufficiency of the heart. Cor Vasa 1961;3:161–77.

58. Katz LN, Schaffer AB. Hemodynamic aspects of congestive heart failure. In: Blumgart H, ed. Symposium on Congestive Heart Failure. 2nd ed. Monograph No. 1, Dallas, Texas: American Heart Association, 199:12–31.

59. Cooley DA, Reul GJ, Wukasch DC. Ischemic contracture of the heart: stone heart. Am J Cardiol 1972;29:571–3.

60. Katz AM, Tada M. The "stone heart": a challenge to the biochemist. Am J Cardiol 1972;29:578–80.

61. Linzbach AJ. Über das Langenwachstum der Herzmuskelfasern und ihrer Kerne in Beziehung zur Herzdilatation. Virchows Arch Pathol Anat Physiol Klin Med 1956;328:165–81.

62. Weber KT, Janicki JS, Schroff SG, Pick R, Chen RM, Bashey RI. Collagen remodeling of the pressure-overloaded, hypertrophied nonhuman primate myocardium. Circ Res 1988;62:757–65.

63. Bristow MR, Ginsburg R, Minobe WA, et al. Decreased catecholamine sensitivity and β-adrenergic receptor density in the failing heart. N Engl J Med 1982;307:205–11.

64. Alpert NR, Gordon MS. Myofibrillar adenosine triphosphatate activity in congestive heart failure. Am J Physiol 1962;202:940–6.

65. Katz AM. Contractile proteins of the heart. Physiol Rev 1970;50:58–163.

66. Swynghedauw B. Developmental and functional adaptation of contractile proteins in cardiac and skeletal muscles. Physiol Rev 1986;66:710–71.

67. Emerson CP Jr, Bernstein SI. Molecular genetics of myosin. Annu Rev Biochem 1987;56:695–726.

68. Breitbart RE, Andreadis A, Nadal-Ginard B. Alternative splicing: a ubiquitous mechanism for the generation of multiple protein isoforms from single genes. Annu Rev Biochem 1987;56:467–95.

69. Lompre AM, Schwartz K, D'Albis A, Lacombe G, Van Thiem N, Swynghedauw B. Myosin isoenzyme redistribution in chronic heart overload. Nature 1979;282:105–7.

70. Rupp H. The adaptive changes in the isoenzyme pattern of myosin from hypertrophied rate myocardium as a result of pressure overload and physical training. Basic Res Cardiol 1981;76:79–88.

71. Scheuer J, Malhotra A, Hirsch C, Capasso J, Schaible TF. Physiologic cardiac hypertrophy corrects contractile protein abnormalities associated with pathologic hypertrophy in rats. J Clin Invest 1982;70:1300–5.

72. Litten RZ, Martin BJ, Low RB, Alpert NR. Altered myosin isozyme pattern from pressure-overloaded and thyrotoxic hypertrophied rabbit hearts. Circ Res 1982;50:856–64.

73. Tsuchimochi H, Kuro-o M, Takaku F, et al. Expression of myosin isozymes during the developmental stage and their redistribution induced by pressure overload. Jpn Circ J 1986;50:1044–52.

74. Izumo S, Lompre A-M, Matsuoka R, et al. Myosin heavy chain messenger RNA protein isoform transitions during cardiac hypertrophy. J Clin Invest 1987;79:970–7.

75. Bugaisky L, Zak R. Biological mechanisms of hypertrophy. In: Ref. 7: 1491–506.

76. Mercadier JJ, de la Bastie D, Menasche P, et al. Alpha-myosin heavy chain isoform and atrial size in patients with various types of mitral valve dysfunction: a quantitative study. J Am Coll Cardiol 1987;9:1024–30.

77. Schwartz K, de la Bastie D, Bouveret P, et al. α-skeletal muscle actin mRNA's accumulate in hypertrophied adult rat hearts. Circ Res 1986;59: 551–5.

78. Izumo S, Nadal-Ginard B, Mahdave V. Protooncogene induction and reprogramming of cardiac gene expression produced by pressure overload. Proc Natl Acad Sci USA 1988;85:339–43.

79. Fox AC. High-energy phosphate compounds and LDH isozymes in the hypertrophied right ventricle. In: Alpert NR, ed. Cardiac Hypertrophy. New York: Academic, 1971:203–12.

80. Meerson FZ, Javick MP. Isozyme pattern and activity of myocardial creatine phosphokinase under heart adaptation to chronic overload. Basic Res Cardiol 1982:77:349–58.

81. Ingwall JS, Kramer MF, Fifer MA, et al. The creatine kinase system in normal and diseased human myocardium. N Engl J Med 1985;313:1050–4.

82. Charlemagne D, Maixen J-M, Preteseille M, Lelievre LG. Ouabain binding sites and (Na^+, K^+)-ATPase activity in rat cardiac hypertrophy: expression of neonatal forms. J Biol Chem 1986;261:185–9.

83. Gwathmey JK, Copelas L, MacKinnon R, et al. Abnormal intracellular calcium handling in myocardium from patients with end-stage heart failure. Circ Res 1987;61:70–6.

84. Wexler LF, Lorell BH, Monomura S-i, Weinberg EO, Ingwall JS, Apstein CS. Enhanced sensitivity to hypoxia-induced diastolic dysfunction in pressure-overload left ventricular hypertrophy in the rat: role of high-energy phosphate depletion. Circ Res 1988;62:766–75.

85. Svedberg K, Hjalmarson A, Waagstein F, Wallentin I. Prolongation of survival in congestive cardiomyopathy by beta-receptor blockade. Lancet 1979;i:1374–6.

86. Furberg CD, Hawkins CM, Lichstein E. Effect of propranolol in postinfarction patients with mechanical or electrical complications. Circulation 1984;69:761–5.

87. 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;55:471–5.

88. Engelmeier RS, O'Connell JB, Walsh R, Rad N, Scanlon PJ, Gunnar RM. Improvement in symptoms and exercise tolerance by metoprolol in patients with dilated cardiomyopathy: a double-blind, randomized, placebo-controlled trial. Circulation 1985;72:536–46.

89. Gilbert EM, Anderson JL, Deitchman D, Mealey P, et al. Chronic beta blockade with bucindolol improves resting cardiac function in dilated cardiomyopathy. Circulation 1987;76(suppl IV):IV-358.

90. The German and Austrian Xamoterol Study Group. Double-blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. Lancet 1988;1:489–93.

91. Packer M. Vasodilator and inotropic drugs for the treatment of chronic heart failure: distinguishing hype from hope. J Am Coll Cardiol 1988;12:1299–317.