INTERNAL MEDICINE GRAND ROUNDS

SEPTEMBER 7, 1989

THE PREVENTION OF CONGESTIVE HEART FAILURE: LEFT VENTRICULAR DILATATION AND ITS MANAGEMENT

Brian G. Firth, MD, D. Phil.

INDEX

I. INTRODUCTION

Congestive heart failure (CHF) affects two to four million Americans, or approximately 2% of the United States population (1). Despite advances in its diagnosis and treatment, the prognosis of CHF remains poor; of 400,000 patients who develop CHF each year, more than 50% die within five years (2-4). These statistics are similar to those reported nearly 20 years ago (5), suggesting that the prognosis of CHF has not improved with conventional drug therapy, including digitalis and diuretics. The aging of the population is only likely to aggravate this problem, since the prevalence of CHF approximately doubles for each succeeding decade from the 4th to the 8th decades of life (6).

A wide variety of congenital or acquired conditions may produce systolic, diastolic, or combined systolic and diastolic dysfunction of the left ventricle (7). However, hypertension and coronary artery disease are generally held to be the most important antecedent factors for the development of CHF in the United States (7,8). Congestive heart failure may ensue following severe segmental damage to the left ventricle after one or more myocardial infarctions. As illustrated diagrammatically (Figure 1), it is possible to intervene at many different stages in the pathophysiological process. This review will focus on the question of left ventricular dilatation and remodelling following myocardial infarction and how this process may potentially be modified to prevent the occurrence of overt CHF.

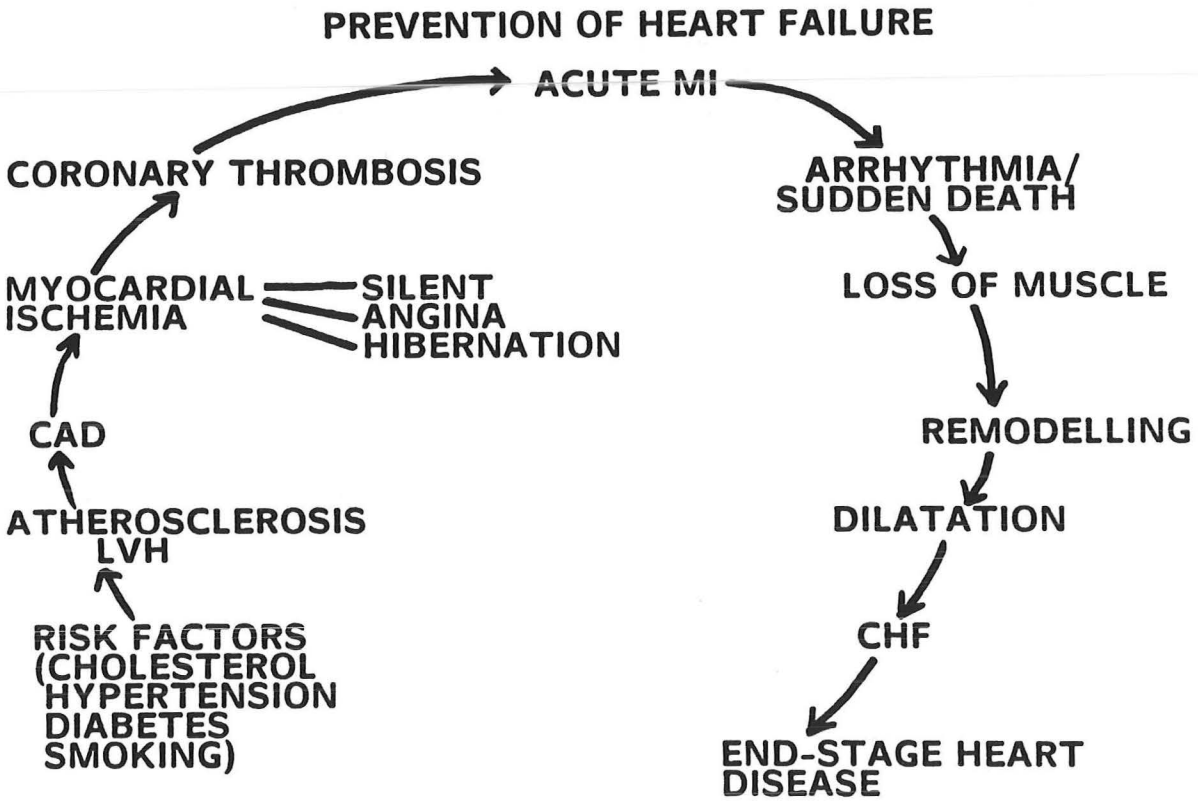


Figure 1. The antecedents of congestive heart failure and possible steps at which the process may be interrupted (after Dzau).

II. THE IMPORTANCE OF LEFT VENTRICULAR DILATATION

A minority of patients will develop overt heart failure in the setting of their first, acute, myocardial infarction. However, by 5 years 14% and by 10 years 22% of such patients will have developed CHF (2). Late heart failure may occur as a result of further myocardial infarction, with a further loss of functional myocardium, or as a result of dilatation and remodelling of the heart.

The amount of myocardium that is irreversibly damaged following one or more myocardial infarctions is the single greatest determinant of long-term survival (9). While the left ventricular ejection fraction has been widely used as an index of residual myocardial function post-infarction, Hammermeister et al suggested 10 years ago that left ventricular volumes may be a more sensitive predictor of outcome than ejection fraction (10).

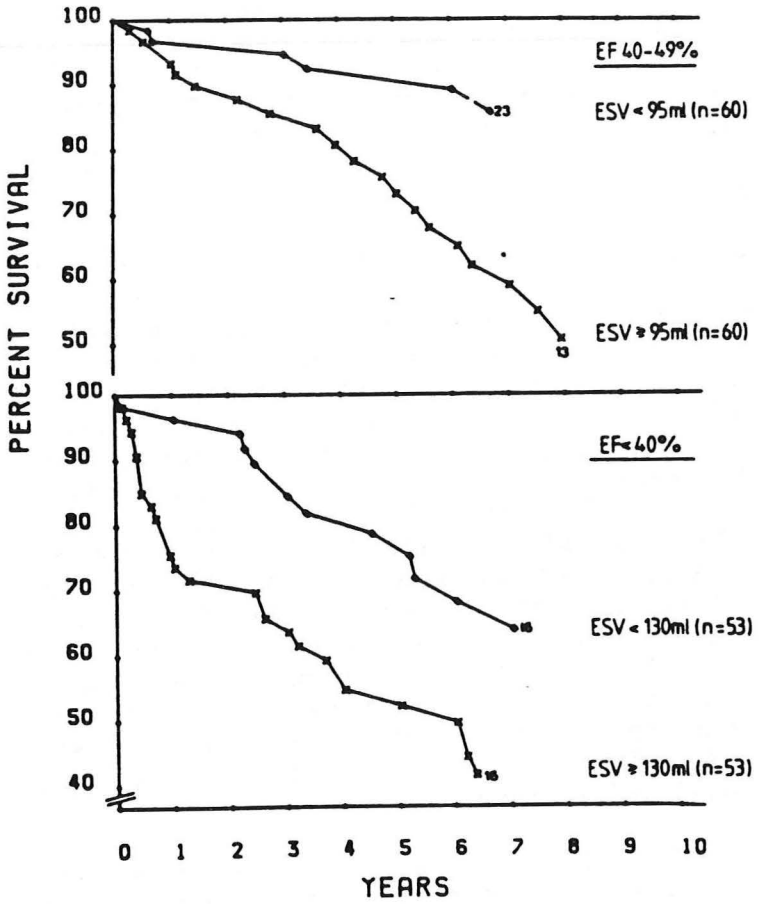


Figure 2. Actuarial survival curves for patients with left ventricular ejection fractions (EF) 40-49% and <40%. Each group is subdivided according to whether end systolic volume (ESV) is above or below the median for that group (Reference #11).

White et al have recently supported this notion by demonstrating that while left ventricular ejection fraction is an important predictor of survival post-infarction, for any given left ventricular ejection fraction patients with larger end-systolic volumes have a worse prognosis over 8

years than those with smaller volumes (11) (Figure 2). Since left ventricular ejection fraction (LVEF) is related to left ventricular volumes by the formula:

$$LVEF = \frac{LVEDV-LVESV}{LVEDV}$$

where EDV is end-diastolic volume, and ESV is end-systolic volume, it is clearly possible to produce a given ejection fraction from widely differing end-systolic and end-diastolic volumes. Thus, the degree of dilatation and remodelling of the left ventricle that occur following myocardial infarction appear to be of cardinal importance.

III. INCIDENCE AND RECOGNITION OF INFARCT EXPANSION

Klein, Herman and Gorlin determined some 20 years ago that stroke volume could not be maintained without ventricular dilatation if more than 20% of the left ventricular wall is destroyed (12). Kitamura et al also drew attention to the geometric and functional abnormalities of the left ventricle that occur with a chronic, localized, non-contractile area (13). Subsequently, Hutchins, Bulkley (Healy) and their associates at Johns Hopkins University, performed a series of seminal studies in humans and a rat model of myocardial infarction, to define the consequences of localized myocardial damage more precisely.

Hutchins and Bulkley (14) were the first to draw attention to the difference between infarct extension (histologically more recent foci of contraction band necrosis around an infarct) and infarct expansion (acute dilatation and thinning of the area of infarction not explained by additional myocardial necrosis). They studied 76 consecutive acute myocardial infarcts aged 30 days or less at autopsy. Infarct extension was found in only 13 infarcts (17%) but infarct expansion was present in 45 infarcts (59 percent). Clinically diagnosed infarct "extension", manifested by new pain, ST segment elevation, rise in serum creatine kinase level and increased congestive heart failure occurred in 14 of the 76 patients (18 percent). At autopsy, these clinical "extensions" were associated with expansion alone in three patients, with extension alone in two, and with both in nine. Severe expansion did not occur until 5 days post-infarction. Histologic examination showed that the thinning of the infarct could not be accounted for by mere removal of necrotic myocardium by inflammatory and reparative responses in infarcts less than 1 week of age. The risk of infarct expansion appeared to be greatest in first, transmural myocardial infarctions.

In a subsequent study, Eaton et al performed serial two-dimensional echocardiographic studies in 28 patients within 14 days of acute infarction (15). They observed a progressive increase in infarct segment length in 8 patients, whom they designated "expanders" but essentially no change in infarct segment length in the remaining 20 patients (Figure 3). Although the 8 patients with infarct expansion did not have significantly higher peak creatine kinase concentrations or greater incidence of congestive heart failure at presentation, they had a significantly greater eight-week mortality (four of eight versus none of 20; $p<0.004$). Infarct expansion was again noted to occur predominantly in those with larger, transmural, anterior or anteroseptal infarcts. Expansion could be detected by 3 days post-infarction and appeared to continue through at least the first 14

days. In this study, the authors suggested that dilatation and expansion affected only the infarct region. However, in a subsequent study by these investigators involving 13 patients with transmural anterior myocardial infarction, which extended for 3-30 months post-infarction, lengthening of both the infarcted segment and the uninfarcted segment was observed (16). Seven of these 13 patients showed evidence of infarct expansion by two-dimensional echocardiography, and the segmental dilatation rate averaged approximately 1 mm/month for both the infarcted (anterior wall) and noninfarcted (posterior wall) segments, respectively. *Thus, left ventricular dilatation, when it occurs, seems to involve stretching of both the infarcted and uninfarcted portions of the myocardium.*

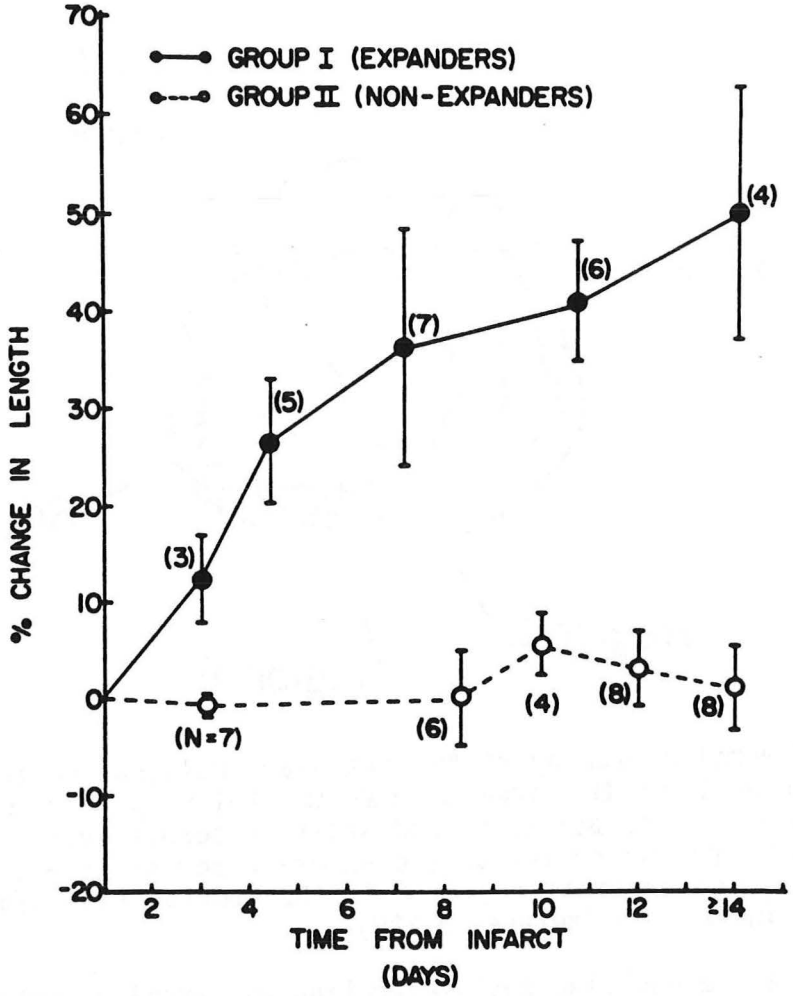


Figure 3. Changes in length of infarcted segments for groups I and II, given as a percentage of change from initial length, as a function of time (Reference #15).

On the basis of these and other (17,18) observations it seems that myocardial infarct expansion, with resultant left ventricular dilatation, begins within 24 hours of acute infarction, occurs in 35-40% of anterior transmural infarcts, is over-represented among patients who die within 30 days of myocardial infarction, occurs with lower incidence with transmural infarcts at other sites, and rarely if ever occurs with non-transmural infarcts (19).

IV. ANIMAL MODELS OF INFARCT EXPANSION AND DILATATION

The incidence of infarct expansion in various animal models depends on the species studied. Dogs have a rich collateral circulation and coronary ligation rarely leads to large, transmural infarctions, unless there is prior or concomitant embolization of the collateral circulation (20). Consequently, infarct expansion is almost never seen in the canine model after simple coronary ligation. Conversely, rats have a poorly developed collateral circulation. Consequently, large transmural infarcts are prevalent, and the incidence of expansion is 60% to 70%.

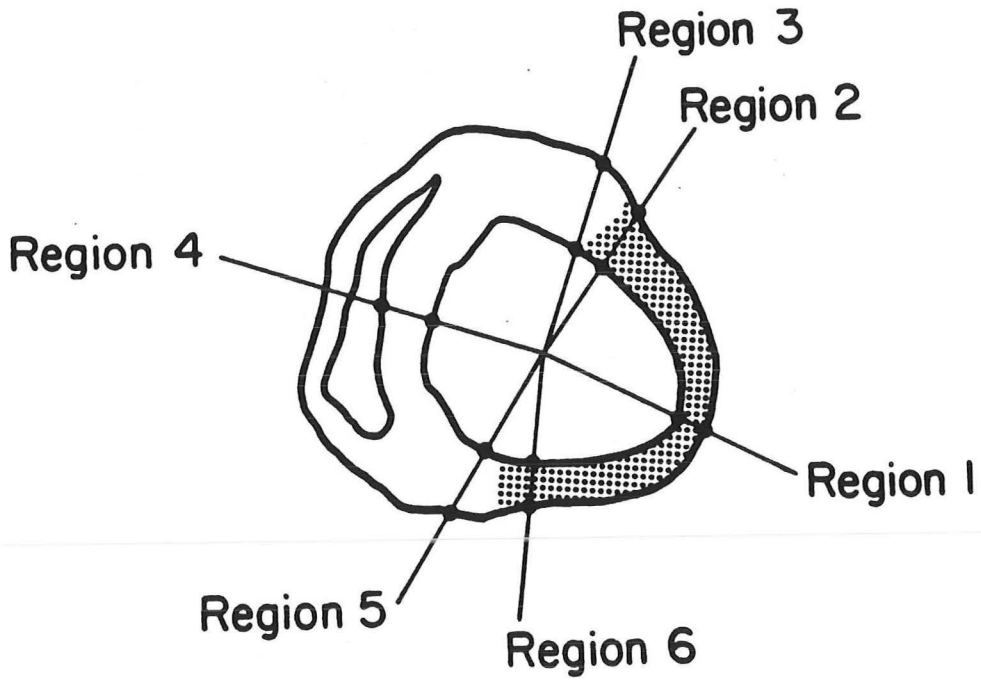


Figure 4. Schematic drawing of the rat heart designating the six regions analyzed: region 1 is the area of maximal thinning within the infarct; regions 2 and 6 are the posterior and anterior border zones, respectively; regions 3 and 5 are the posterior and anterior border zones, respectively, just outside of the infarct; region 4 is the remote, non-infarcted septum. Shaded area = infarction (Reference #29).

Myocardial remodelling post-infarction was studied further by Weisman et al in a rat model of myocardial infarction (21). Ligation of the intramural left coronary artery produced transmural infarcts in 45 rats, which were killed on days 1, 2 and 3 post-infarction. (In the rat, ligation of the left coronary artery does not result in septal infarction, and histopathological changes, myocardial thinning, dilatation and remodelling occur about twice as rapidly as in man). Twenty-eight of these 45 rats developed infarct expansion. Detailed structural evaluations were performed on the transverse section of each heart by designating six adjacent regions (Figure 4) as follows: (1) The region of maximal thinning in the infarct zone; (2) the posterior border zone inside of the infarct; (3) the posterior border zone outside of the infarct; (4) the midseptal area most remote from the infarct; (5) the anterior border zone outside of

the infarct; and (6) the anterior border zone inside of the infarct. Wall thinning was consistently greater in the infarct zone, with a 55% decrease from normal, than in the non-infarct regions which showed a 28% decrease from normal ($p<0.001$). In order to assess the degree of dilatation of these hearts, regional radii of curvature were constructed. As with wall thickness, all regions were affected and the extent of dilatation increased as expansion increased in severity ($p<0.01$). Using analysis of covariance, these authors also examined the independent effects of expansion and infarct size on regional wall thickness. For each region, wall thickness significantly correlated with expansion ($p<0.001$) but not with infarct size. The 17 rats without infarct expansion had a mean infarct size of $22\pm2\%$ of left ventricular mass, which was significantly smaller than that of the rats with infarct expansion: mean infarct size as a percentage of left ventricular mass was $35\pm4\%$ for those with 1+, $42\pm5\%$ for those with 2+, and $45\pm5\%$ for those with 3+ to 4+ expansion. *Thus, it appears that infarct size does have a bearing on the occurrence of infarct expansion, but beyond a certain size, other factors may determine the severity of expansion.*

V. FACTORS THAT MAY AGGRAVATE DILATATION

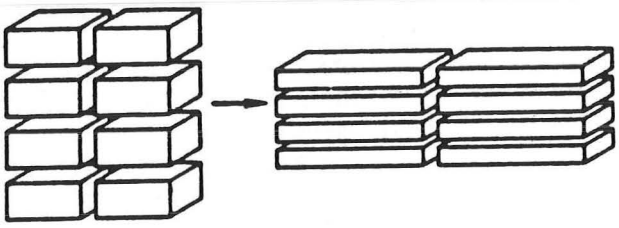
Since infarct size does not seem to be the sole determinant of the severity of infarct expansion after myocardial infarction, Nolan et al investigated the effect of increased afterload on this process (22). Forty rats were randomized to aortic banding (n=20) or sham operation (n=20) and allowed to recover for 3 weeks. At that time, they were again randomized to left coronary artery ligation (n=30) or sham operation (n=10). Seven days later these rats were sacrificed and the morphological changes involving the myocardium were characterized. Infarct size, as a percent of left ventricular mass, was less at the time of death in the group with aortic banding. However, infarct expansion, as measured by cavity dilatation and infarct thinning, occurred in both infarct groups but was greater in the group with aortic banding. To what extent the increase in afterload *per se* as opposed to the resultant myocardial hypertrophy was responsible for these effects is uncertain. It is also not certain how the findings of this study of the effects of a short-term increase in afterload relate to the clinical counterpart, namely chronic systemic arterial hypertension. Nevertheless, it appears to be consistent with the findings of Pierard et al (23) who found a higher incidence of infarct expansion in those with previous systemic hypertension, and with the observation that myocardial rupture, which occurs as a sequela of infarct thinning and expansion, is more common in patients with systemic arterial hypertension (24). In addition to hypertension, certain drugs, including corticosteroids and non-steroidal antiinflammatory agents may aggravate the process (25-27).

A variety of other local factors, to be discussed later, may possibly contribute to left ventricular dilatation post-infarction (28).

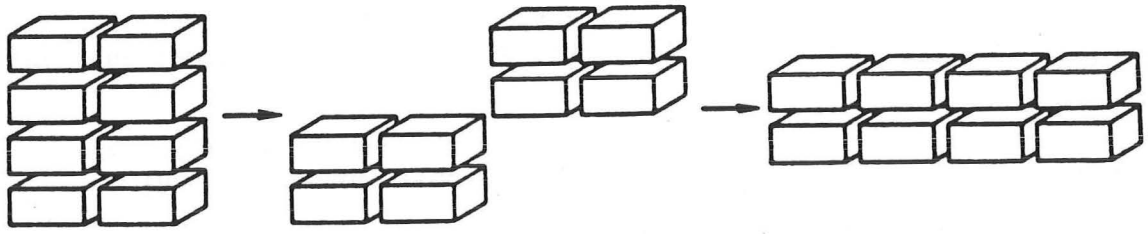
VI. HISTOPATHOLOGIC MECHANISM OF INFARCT EXPANSION

Since infarct expansion is seen in the first few days following myocardial infarction, before significant removal of necrotic myocytes or proliferation of connective tissue, loss and replacement of myocardium cannot explain the thinning and dilatation that occurs. There are several

potential mechanisms to explain the observed dilatation and thinning that occurs in association with infarct expansion. These include: (1) cell rupture; (2) a reduction in the intercellular space; (3) stretching of myocytes; or (4) slippage of groups of myocytes so that fewer cells are distributed across the wall (Figure 5). In order to determine the relative contribution of these four mechanisms, Weisman et al (29) performed detailed studies of transverse sections of rat hearts with infarct expansion at 1, 2, and 3 days after coronary ligation. The number of cells across the wall was determined in the six previously defined adjacent regions (see Figure 5). Cell counting was performed so that the total number of cells across the wall as well as the number of cells per unit wall thickness (cell density) could be determined. The transmural cell count and the cell density were then correlated with the wall thickness in each region. Myocyte cross-sectional areas and sarcomere lengths were also measured. The results of the infarct expansion hearts were compared with those of sham-operated control hearts. When compared with controls, all regions of the rat infarct expansion hearts showed wall thinning ($p<0.001$) but this was most pronounced in the infarct zone. There was a decrease in the number of cells across the myocardial wall accompanying the wall thinning at each site ($p<0.0001$). The change in cell number correlated closely with the change in wall thickness ($r=0.915$; $p<0.001$). In the noninfarcted regions, cell slippage accounted for all the thinning. However, in the infarct zone, up to 20% of the thinning that occurred was attributable to a combination of cell stretch and decrease in intercellular space, while the remainder was due to cell slippage. Ultrastructural studies with electron microscopy confirmed that intramyocardial rupture did not occur within the infarct zone of the hearts with infarct expansion.



1. CELL STRETCH: LENGTHENING AND THINNING OF MYOCYTES



2. CELL SLIPPAGE: REARRANGEMENT OF CELLS OR GROUPS OF CELLS IN SUCH A WAY THAT THERE ARE FEWER CELLS ACROSS THE WALL

Figure 5. Cellular mechanisms of infarct expansion (Reference #19).

In order to determine whether these observations hold true for man as well these investigators performed similar histological studies on the hearts of 5 patients who died within 3 days of infarction and 2 hearts of patients who died without obvious coronary disease. As in the rat, there was a striking correlation between the number of cells across the wall and wall thickness ($r=0.94$, $p<0.001$).

VII. HYPERTROPHY OF THE NONINFARCTED MYOCARDIUM

Several different groups of investigators have recently demonstrated that hypertrophy of the noninfarcted myocardium occurs in response to myocardial infarction (22,30-32). In the previously described rat model of myocardial infarction reported by Nolan et al (22), the authors estimated that the volume of the noninfarcted myocardium increased by 13.1% in response to coronary ligation and infarction ($p<0.05$). Although precise quantitation of the degree of hypertrophy that occurs presents technical problems, it nevertheless seems clear that hypertrophy of the noninfarcted myocardium is a real occurrence.

It is easy enough to provide a teleological explanation for the observed hypertrophy, namely, that it occurs in order to "compensate" for the loss of functional myocytes in the infarct zone. However, it is likely that what starts as a <u>physiological</u> process ultimately becomes a <u>pathological</u> process.

VIII. PHYSIOLOGIC VERSUS PATHOLOGIC HYPERTROPHY

Cardiac hypertrophy is an increase in mass of the heart due to an increase in cell volume of the individual cardiac myocytes in the organ (33). <u>Physiologic hypertrophy</u> of myocytes occurs typically during growth or as a result of strenuous exercise; <u>pathologic hypertrophy</u>, on the other hand, is usually associated with chronic severe work overload of the heart (34). In addition to altered contractile function of the heart, there is a decreased rate of myosin adenosine triphosphatase (ATPase) activity (34,35).

The most remarkable increase in heart muscle size occurs during normal growth. Cardiac myocytes in the rat or the dog show a 30-35 fold increase in cell volume during normal growth (36,37). Furthermore, the volume percent composition of various organelles within the growing cell remains constant (38). Although few quantitative studies have been conducted on the hearts of animals with physiologic hypertrophy due to strenuous exercise, there does not appear to be a significant change in organelle composition of the heart in such animals.

During the early phases of certain pathologic conditions, there may be a physiologic hypertrophy, which may or may not be accompanied by temporary changes in organelle content. In early stages of sudden pressure-overload-induced cardiac hypertrophy in experimental animals, there may be a relative increase in the volume percent of mitochondria in the heart muscle tissue (39,40). This is accompanied by an increase in cardiac function, which was originally described by Meerson as *the stage of cardiac hyperfunction* (41). Once stabilization of hyperfunction occurs,

mitochondrial volume percent return to normal or reduced levels in the hypertrophied myocyte, even in the absence of myocardial failure (42,43).

Compensatory hypertrophy occurs when there is loss of myocardium in a single large focal area, or in a diffuse or multifocal manner (33). The classic example in man is acute myocardial infarction where the remaining myocardium is required to do the work previously performed by the entire heart, and hence undergoes physiologic hypertrophy. In later stages of compensatory hypertrophy, myocardial decompensation and failure occur i.e. there is pathologic hypertrophy. There is currently much speculation as to why this compensatory hypertrophy contributes to rather than prevents the occurrence of overt heart failure. Some of the current concepts on this matter will be detailed below.

A. Structural Factors

(1) Intercapillary diffusion distance

The intercapillary diffusion distance is of necessity increased as heart muscle cells increase in cross-sectional area. If the number of capillaries relative to the number of fibers does not change, as seems to be the case, the number of capillaries per unit area of muscle tissue will be decreased (44). This results in an increased diffusion distance between capillaries. That this may be a mechanism for the development of myocardial failure in the presence of severe cardiac hypertrophy has been suggested since the 1930s (45). However, there is no proof that this is in fact an important mechanism, although it seems plausible. If this mechanism is indeed of importance, it may be aggravated by the accumulation of components such as collagen, fibroblasts, macrophages, edema and amyloid. Interstitial collagen deposition, in particular, has been suggested as a contributing factor to the ventricular dysfunction that may occur with compensatory hypertrophy (46,47).

(ii) Chronic subendocardial ischemia

The possible role of cardiac hypertrophy in the development of chronic subendocardial ischemic lesions remains speculative. Nevertheless, in the setting of chronic experimental cardiac hypertrophy coronary blood flow reserve appears to be reduced (37,48). There is likewise evidence of limited coronary reserve in humans with left ventricular hypertrophy due to aortic stenosis (49) or a dilated cardiomyopathy (50). While there are no data to indicate whether such limited vasodilator reserve is present in man in association with the compensatory hypertrophy that occurs in the uninfarcted region of the myocardium, depressed coronary vasodilator reserve has been demonstrated in this region in a rat model of myocardial infarction (51). Whether this limitation of cardiac flow in the hypertrophied, uninfarcted region of the myocardium is causally linked to the pathogenesis of left ventricular failure is uncertain.

(iii) Energy deprivation

Katz (52) has repeatedly stressed the fact that the failing heart may be energy starved and be operating under a condition of anaerobiosis. With the development of established myocardial hypertrophy, the fraction of cell

volume occupied by myofibrils increases, whereas the mass of mitochondria decreases (53,54). The resulting disproportionate increase in the volume fraction of the cardiac myocyte occupied by energy-consuming myofibrils, relative to the volume of mitochondria, which regenerate adenosine triphosphate (ATP), could contribute to a deficit of chemical energy in the failing heart. Furthermore, animal models of heart failure show evidence of decreased myocardial high-energy phosphate content after pressure overloading of the left and right ventricles (55,56). Endomyocardial biopsies from the hearts of patients with CHF also suggest a correlation between the decrease in ATP content and the impairment in contraction and relaxation (57). Thus, energy deprivation in the uninfarcted, hypertrophied myocardium, may contribute to this region of the heart becoming dysfunctional.

B. Alterations in myosin isoforms

In response to increased demand, the heart responds with an increase in mass and a commensurate increase in the size of individual myocytes. This increase in mass can only occur if the net rate of protein synthesis exceeds the net rate of protein degradation. Morgan et al (58,59) have shown clearly that increased aortic pressure, and the attendant stretch of the heart muscle (increase in wall tension) are the mechanical parameters most closely associated with faster protein synthesis. Exactly how the nuclear protein synthetic machinery deciphers the signal is poorly understood.

Several investigators have studied the effects of stimuli (e.g. aortic banding, thyroid hormone administration) that are known to produce myocardial hypertrophy associated with quantitative and qualitative alterations in myosin gene expression and protein production. There are three isoenzymes of myosin: the V_1 myosin, which is a homodimer made up of two alpha heavy chains; the V_3 myosin, which is a homodimer made up of two beta chains; and the V_2 isoenzyme, which is a heterodimer consisting of one alpha and one beta chain (60). V_1 has a higher Ca^{2+}-ATPase activity than does V_3 (61). In rabbits, the V_3 isoform predominates in late fetal life. Soon after birth, the V_1 form (high ATPase activity) predominates. However, in very old rabbits, the V_3 (low ATPase activity) form again predominates. In response to thyroid hormone stimulation, there is a relative increase in the V_1 isoenzyme with a commensurate increase in its mRNA (62). These data are consistent with thyroid hormone regulating the synthesis of ventricular myosin at steps that precede translation of its message. Umeda et al (63) have recently demonstrated that the control of myosin heavy chain expression in cardiac hypertrophy is regulated primarily by the rate of gene transcription.

In response to pressure overload, Rappaport et al (64) have demonstrated that in small rodents, during the development of hypertrophy, a redistribution of these myosin isoenzymes occurs, with a predominance of V_3 in the largest hearts and an intermediate pattern in the less affected hearts (Figure 6). This increase in V_3 isoenzyme results in a decrease in overall ATPase activity. A significant negative correlation also exists between the maximum velocity of shortening, as measured using a papillary muscle and the quick-release technique, the decrease in V_1 (high ATPase myosin isoenzyme), and the decrease in myosin ATPase activity (65).

Unfortunately, the change in heavy chain myosin isoenzymes in small rodents cannot explain the decrease in contractile function in man, since the adaptational process at the isomyosin level is small or non-existent (64). In human hearts, the V_3 (low ATPase activity) isoenzyme predominates with the V_1 isoenzyme accounting for only 1% of heavy chain myosin. This pattern appears to be unchanged in the overloaded myocardium (66).

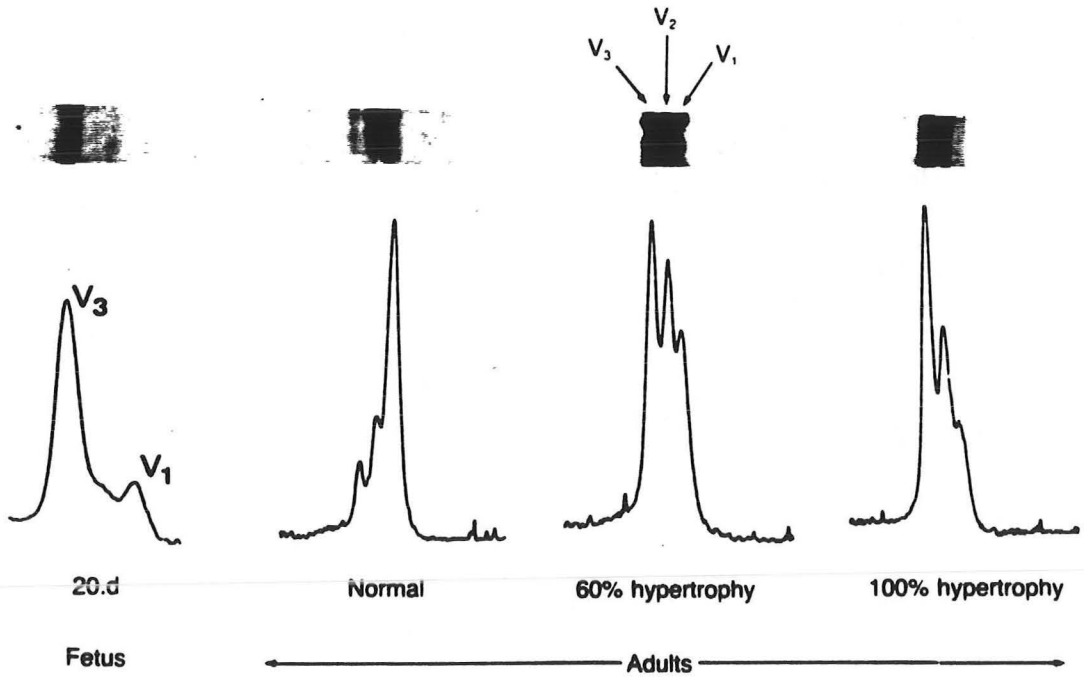


Figure 6. Ventricular myosin isoenzyme redistribution in cardiac overload. Pyrophosphate gel electrophoresis shows the three myosin isoenzymes. The fetal predominant isoform, V_3 (on left, 20 day old fetus) reappears in chronic overload. The 60% hypertrophy was obtained 1 month after aortic stenosis; 100% hypertrophy was obtained 2 months after aortic stenosis (Reference #64).

C. The myocardial intracellular renin-angiotensin system

The renin-angiotensin system is traditionally viewed as a circulating hormonal system dedicated to the regulation of intravascular volume and systemic blood pressure. However, it has recently become apparent that there are multiple local, intracellular systems capable of generating angiotensin II from angiotensinogen (67). Dzau and Re (68) have recently demonstrated the presence of renin in isolated mouse and rat myocytes. In addition to its endocrine effects, there is now mounting evidence that the renin-angiotensin system may subserve a local role (69). This role may be

paracrine e.g. locally secreted angiotensin II in the heart could affect catecholamine release by local nerves and thereby alter contractility. In addition, there could be autocrine functions whereby the secreted angiotensin II could feed back on its cells of synthesis to regulate such events as renin synthesis or even cellular growth. Finally, there may be intracrine functions i.e. an action of the peptide hormone in its cell of synthesis. Intracellularly generated angiotensin II has been shown to interact with specific high affinity acceptors and produce changes in chromatin structure. Although there is at present no direct evidence for increased protein synthesis by cardiac myocytes in response to angiotensin, it is known to increase protein synthesis in hepatocytes. Thus, the intracellular renin-angiotensin may potentially play a role in the genesis of myocardial hypertrophy apart from any effects that the circulating renin-angiotensin system may have on cardiac function. Whether this results in an improvement or a worsening of contractile function is unknown.

D. The beta-adrenergic receptor pathway

The contractile state of the heart is under direct control of the adrenergic nervous system. Both beta-adrenergic and alpha-adrenergic receptors are present in myocardial cells and serve to link hormone-mediated chemical signals to the mechanical event of increased myocardial contractility. In the normally functioning human heart, the beta-adrenergic receptor system mediates the greatest amount of inotropic support. It is not surprising that beta-adrenergic mechanisms play an important role in supporting contractile function when the heart suffers diffuse or segmental injury (70).

The beta-adrenergic receptors, located on the surface of the sarcolemma, are linked via the stimulatory guanine nucleotide regulatory protein (G_s) to the enzyme adenylate cyclase (71) (Figure 7). The receptor can exist in a low affinity state for agonist binding that is "uncoupled" from adenylate cyclase. In its high affinity state it can associate with and stimulate G_s, which ultimately activates adenylate cyclase with a resultant increase in intracellular cyclic AMP (cAMP). Formed cAMP may then activate one of several protein kinases with resulting phosphorylation of target structures e.g. myosin ATPase, calcium channels. An increased cytosolic cAMP concentration consequently produces an increase in myocardial contractility. The activated G_s alpha subunit may also directly activate the cell-surface calcium channels (72).

Multiple lines of evidence, well summarized by Bristow et al (70), point to the fact that in the face of mild myocardial damage e.g. segmental tissue loss due to infarction, adrenergic augmentation of the contractile state of the remaining, viable cells plays a role. However, as heart failure ensues, there is an increase in circulating norepinephrine and myocardial beta-receptors become "desensitized" to the elevated circulating levels of catecholamines (73). In chronic heart failure, the myocardium also becomes refractory to exogenously administered beta-adrenergic agonists and shows a characteristic blunted responsiveness (74,75). In addition, to the reduction in beta-adrenergic receptor number noted in tissue obtained from the failing human heart (70), a marked decrease in high-affinity beta-adrenergic binding sites has been demonstrated in a

canine model of congestive heart failure (76). Interestingly, in Vatner's canine model of heart failure, there was actually an <u>increase</u> in beta-adrenergic receptor density, but a <u>decreased</u> fraction of the receptors that bind agonist with high affinity, with a resultant decreased adenylate cyclase activity in sarcolemma from the failing hearts (76). In this model of pressure overload left ventricular failure, these investigators demonstrated a 59% reduction in the concentration of the alpha subunit of G_s (G_s alpha) and a 50% reduction in G_s activity (77). Likewise, in the cardiomyopathic Syrian hamster, there is ~50% less G_s activity in both cardiac and skeletal muscle without a significant change in beta-receptor density (78).

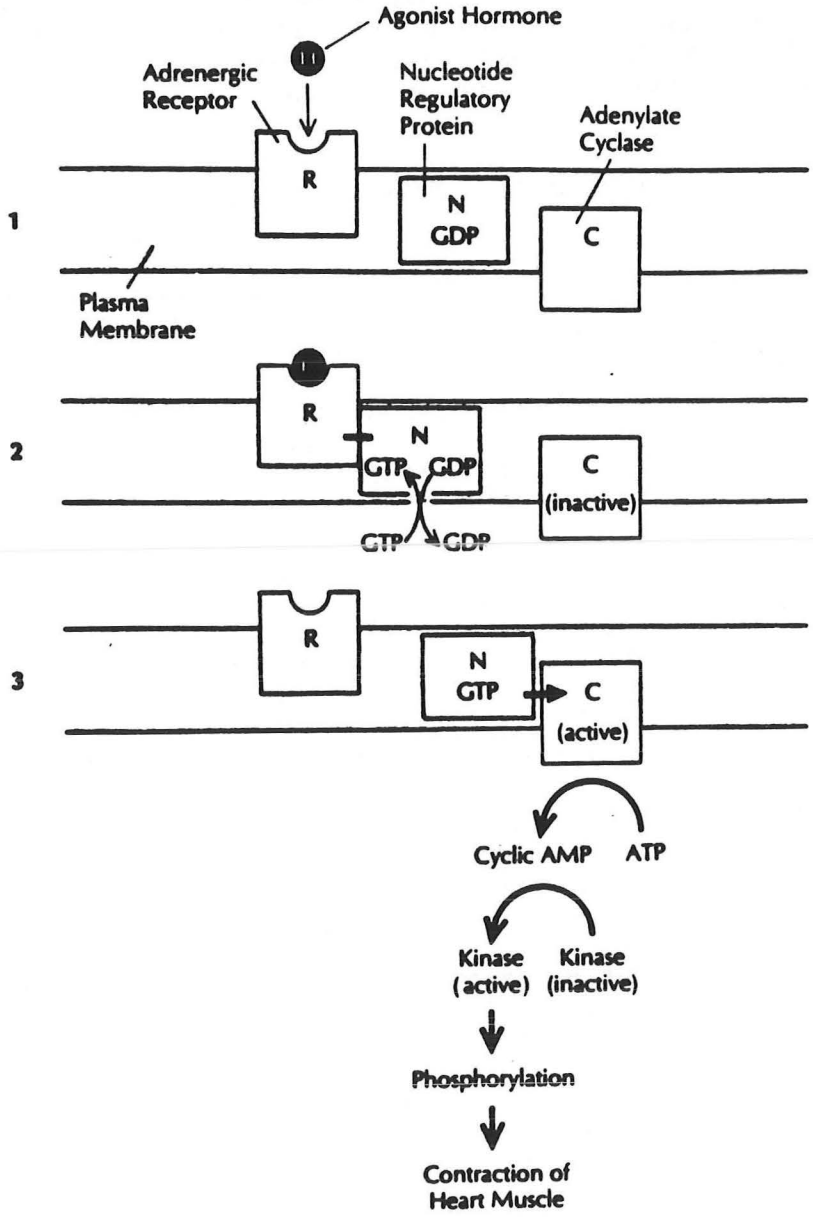


Figure 7. The receptor-effector model for beta-adrenoceptor activity. H=hormone; R=receptor; N=nucleotide regulatory protein; GDP=guanosine diphosphate; GTP=guanosine triphosphate; C=catalytic unit of adenylate cyclase. From Heinsimer JA, Lefkowitz RJ. Hosp Prac 18:115. 1983.

That these observations concerning G_s alterations in animal models of heart failure are applicable to man is suggested by the observations of Horn et al (79). When patients with congestive heart failure were compared to age and sex matched controls, they observed a 40% decrease in beta-adrenergic receptor numbers ($p<0.05$) and an 80% decrease in G_s levels ($p<0.05$) on circulating lymphocytes, which may serve as a surrogate for myocardial tissue. In response to the ACE inhibitors captopril and lisinopril, there was an increase in beta-receptor density (5.5 ± 0.7 to 8.7 ± 1.5 fmol/mg) and a two-fold increase in G_s levels ($p<0.05$), without any significant change in the concentration of circulating norepinephrine. Therefore, it is possible that one mechanism whereby treatment with converting enzyme inhibitors improves cardiac (and possibly skeletal) muscle function may be via an increase in beta-receptor number or an increase in G_s, which may augment beta-adrenergic receptor-adenylate cyclase coupling.

A final consideration with regard to the beta-adrenergic receptor pathway and the manner in which it may be involved in myocardial dysfunction relates to the observed "toxic" effects of catecholamines on the myocardium (70,80). The molecular basis for catecholamine-mediated cardiotoxicity is unclear but probably involves some combination of receptor pathway-mediated calcium overload, exhaustion of high energy phosphate stores, free radical formation, and relative ischemia (70).

In summary, while the beta-adrenergic pathway may serve to augment the function of the remaining myocytes initially, in the setting of compensatory hypertrophy, excessive stimulation of this pathway may ultimately contribute to the decrease in myocardial contractility.

E. The alpha-adrenergic receptor pathway

The alpha adrenergic receptor pathway appears to play an important role in myocyte hypertrophy. The alpha adrenergic receptors are located on the cell surface, and appear to be linked via an as yet undefined guanine nucleotide regulatory protein (G?) to the phosphatidylinositol pathway (Figure 8). Alpha-adrenergic stimulation produces chronotropic and inotropic effects on the heart, which are associated with an increase in phosphatidylinositol turnover, Ca^{2+} flux, and inhibition of cAMP phosphodiesterase activity (81). In addition, Simpson (82) first demonstrated that hypertrophy of cultured neonatal rat myocytes occurs in response to norepinephrine stimulation, and that this is an $alpha_1$ receptor mediated response. (The two-fold increase in cell size as well as cell protein content was inhibited by the non-selective alpha-adrenergic antagonist phentolamine and by the $alpha_1$ adrenergic antagonists prazosin and terazosin; it was not inhibited by the beta receptors antagonist propranolol or by the $alpha_2$ adrenergic antagonist yohimbine). In addition, there is an increase in the fractional synthetic rates of contractile proteins (83). Furthermore, using the model of cultured neonatal rat myocardial cells, Lee et al (81) at this institution showed that $alpha_1$-adrenergic stimulation resulted in a several-fold increase in sarcomeric units, as assessed by electron microscopy, an increase in the cellular myosin light chain-2 (MLC-2) content, and a 2-3 fold increase in the steady state levels of MLC-2 mRNA. This effect of alpha-adrenergic stimulation was accompanied by a 2-3 fold increase in total transcriptional

activity, which was dependent on the concentration and duration of exposure to the agonist.

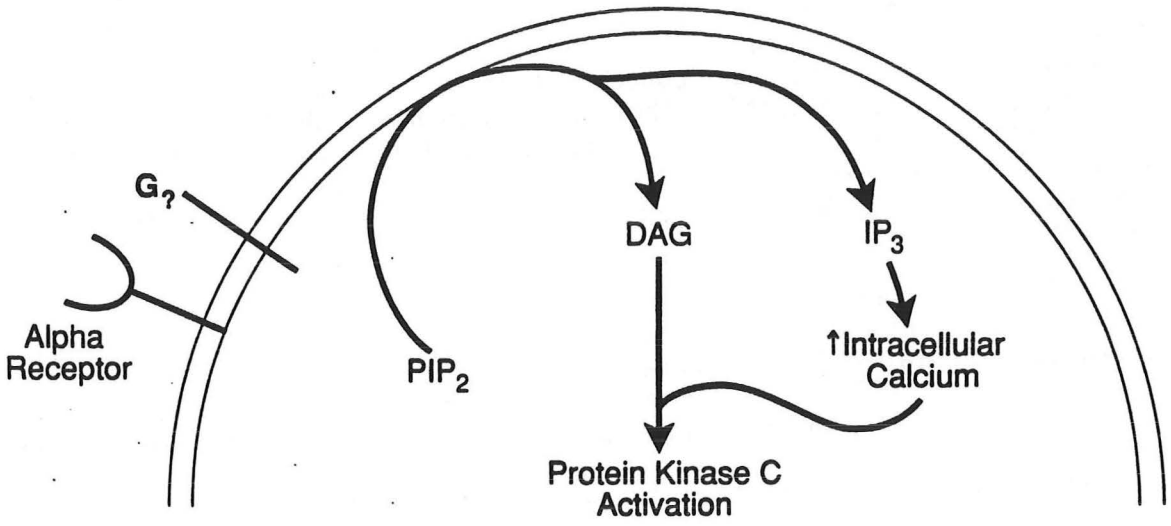


Figure 8. The $alpha_1$ associated neonatal rat myocyte growth responses. G? = undefined G protein; PIP_2 = phosphatidylinositol phosphate; DAG = diacylglycerol; IP_3 = inositol phosphates.

The biochemical mechanisms that link the occupancy of the $alpha_1$-adrenergic receptor with the increase in transcriptional activity are unclear. However, in adult, neonatal and embryonic myocardial cells, phenylephrine stimulates phosphatidylinositol hydrolysis resulting in the formation of diacylglycerol and inositol phosphates. Inositol phosphates in turn stimulate the release of Ca^{2+} from the sarcoplasmic reticulum and, in combination with diacylglycerol, result in activation of protein kinase C (Ca^{2+}/phospholipid-dependent enzyme). Protein kinase C, in addition to phosphorylating contractile proteins and thereby increasing contractility may be important in the generation of the signal for increased transcriptional activity. The evidence for this lies in the observation that tumor-promoting phorbol esters, which <u>directly</u> activate protein kinase C (rather than via the $alpha_1$-adrenergic receptor) can increase the transcriptional activity of cultured neonatal rat myocardial cells (84). Nevertheless, it is of interest that although phorbol ester stimulation of these myocytes produces a similar degree of hypertrophy and protein synthesis to $alpha_1$-adrenergic stimulation, the phorbol-ester stimulated cells contract sluggishly while the phenylephrine ($alpha_1$ agonist) stimulated cells beat vigorously (85). *This observation serves to emphasize yet again that myocyte hypertrophy does <u>not</u> necessarily imply an*

improvement in contractile function - i.e. there may be a dissociation between protein synthesis and contractile behavior.

Finally, there is evidence to support the notion that "dysfunctional contractile proteins" may occur. Investigators in the laboratories of Nadal-Ginard (86) have demonstrated a remarkable diversity of contractile proteins, which appear to be largely the result of alternative RNA splicing of individual contractile protein genes, as well as the result of differential expression of multigene families of contractile proteins.

In summary, while it is clear that compensatory hypertrophy occurs in response to segmental myocardial damage, it is not clear at what point and precisely why this hypertrophy becomes dysfunctional. In all probability, many of the factors enumerated, and probability others as well, play a role in this process.

IX. PREVENTION OF INFARCT EXPANSION AND/OR LV DILATATION

A. Nitroglycerin

Infarct expansion begins to occur early in the post-infarction period. Therefore, it seems possible that interventions applied early in the post-infarct period might prevent infarct expansion. Jugdutt (87) demonstrated that intravenous nitroglycerin, administered 2 hours after coronary occlusion for a period of 6 hours resulted in a significant reduction in infarct size in a canine model of myocardial infarction, provided that mean arterial pressure was not reduced by more than 10% with this intervention. Jugdutt et al (88,89) subsequently showed that prostacyclin and ibuprofen could similarly reduce infarct size in this experimental model. By 1 week, infarct expansion was also reduced by nitroglycerin and prostacyclin; however, unlike nitroglycerin or prostacyclin, ibuprofen aggravated infarct expansion. Ibuprofen had no preload or afterload reducing effects. *Thus, the observed reduction in infarct expansion appeared to be related to the presence of altered loading conditions on the ventricle rather than to a direct effect on infarct size.* Jugdutt and Amy (90) further observed that the nitroglycerin treated animals had a significant increase in hydroxyproline, a marker of collagen content, in the infarct zone when compared to saline treated controls. Thus, nitroglycerin may actually serve to improve wound healing through some as yet undefined mechanism.

Jugdutt and Warnica (91) recently showed that their observations concerning nitroglycerin are applicable to man. They randomized 310 consecutive patients with acute myocardial infarction to nitroglycerin (n=154) or control (n=156) groups. Nitroglycerin was titrated to lower mean arterial blood pressure by 10% in normotensive and 30% in hypertensive patients, but mean blood pressure was not allowed to fall below 80 mmHg. Infusion was continued for a mean of 39.2 hours. Compared to controls, the nitroglycerin treated patients had a significant reduction in infarct size, as measured by creatine kinase, in both anterior and inferior infarctions ($p<0.001$). This effect was more marked in those treated less than 4 hours after the onset of pain than later. By 10 days, echocardiographically determined infarct expansion index had increased by 31% ($p<0.001$) and thinning ratio had decreased by 17% ($p<0.001$) in controls but remained

essentially unchanged in the nitroglycerin treated group. Infarct related complications were also less frequent in the nitroglycerin treated group than the control group: infarct expansion syndrome (2% vs 15%; $p<0.005$), left ventricular thrombus (5% vs 22%, $p<0.005$), cardiogenic shock (5% vs 15%, $p<0.005$), and infarct extension (11% vs 22%, $p<0.025$). In the subgroup with anterior infarction, mortality was lower in the nitroglycerin than the control group in hospital (14% vs 26%; $p<0.01$), at 3 months (16% vs 28%; $p<0.025$), and at 12 months (21% vs 31%, $p<0.05$). The findings in this study make a very strong case for the judicious use of intravenous nitroglycerin early in acute myocardial infarction to limit infarct size, prevent infarct expansion and its sequelae. They serve to further support the beneficial effects of nitroglycerin in this setting demonstrated by other investigators (92,93) and by meta-analysis from the available controlled studies by Yusuf and Furberg (94).

B. Nitroglycerin and Intraaortic Balloon Counterpulsation

If nitroglycerin has beneficial effects on infarct size and infarct expansion, it might be expected that the combined use of intravenous nitroglycerin and intraaortic balloon counterpulsation (which decreases aortic systolic pressure while increasing diastolic perfusion pressure) might be even more beneficial. However, in one small study (95) of 20 patients randomized to this form of therapy or standard treatment, infarct zone expansion was not prevented, but dilatation and remodelling of the noninfarcted segments was prevented during the first 2 weeks after acute myocardial infarction. In this study, intravenous nitroglycerin was commenced at a mean of 8.6 hours after the onset of chest pain and intraaortic balloon counterpulsation an average of 1.9 hours later in the 9 patients who received this form of therapy. The combination of intraaortic balloon counterpulsation and intravenous nitroglycerin resulted in a decrease in systolic arterial pressure of 34 mmHg (25%), an increase in aortic diastolic pressure of 23 mmHg (23%), and a decrease in heart rate of 5 beats/min (5%). Whether the less than dramatic beneficial effect seen with combination therapy in this study was due to the small number of patients studied, the fact that therapy was commenced considerably later than in Jugdutt and Warnica's study (89), or some other factor, is uncertain.

C. Angiotensin Converting Enzyme Inhibitors

The angiotensin converting enzyme inhibitor, captopril, which has both preload and afterload reducing properties, has been shown in a canine model of myocardial infarction to limit the extent of infarction and increase regional myocardial blood flow when administered between 30 minutes and 6 hrs after coronary occlusion (96). The limitation of infarct size is presumably due to the preload and afterload reducing effects of captopril as well as the increase in collateral blood flow to the ischemic zone. However, other mechanisms, such as its free radical scavenging properties (97), its potential effects on the intracellular renin-angiotensin system or nuclear regulating proteins, may play some part.

Overall the available data concerning the beneficial effects of captopril or any other ACE inhibitor treatment in the setting of acute myocardial infarction are more limited than for nitroglycerin. However,

there is mounting evidence that captopril, when commenced 7 to 31 days post-infarction and administered long-term decreases left ventricular dilatation, both in animal models and in man, and may result in improved survival.

In an elegant series of placebo-controlled experiments Pfeffer and associates (98-101) studied the effects of captopril on a rat model of myocardial infarction. In the first series of experiments (98,99), myocardial infarction was produced in normotensive, female Wistar rats by ligation of the left coronary artery. At 2 or 21 days following infarction, the 163 rats who survived surgery were randomized to receive either captopril (2 g/liter of drinking water) or tap water for a period of 3 months. At the end of this time period, baseline hemodynamics and maximum flow generating capability were assessed following volume loading studies. The hearts were then arrested in diastole and the passive pressure-volume relations were determined and infarct size was measured. In untreated rats, left ventricular end-diastolic pressure progressively rose (from 5-28 mmHg) as a function of infarct size, whereas in captopril-treated rats left ventricular filling pressure remained in the normal range (5 ± 1 mmHg), except in those with very extensive infarcts. This occurred despite the fact that myocardial infarct size was not significantly smaller in the captopril treated rats. In addition, peak stroke volume index and ejection fraction were significantly higher and ventricular volumes were smaller in the captopril treated rats than in the placebo-treated controls. The left ventricular chamber stiffness (pressure-volume relationship) was also normalized by captopril treatment.

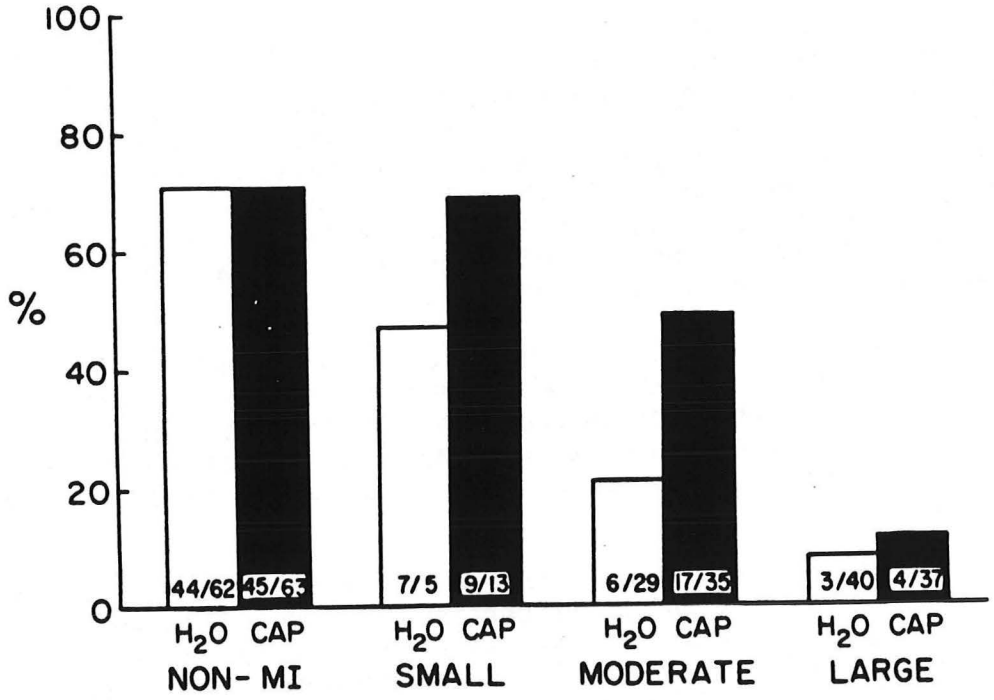


Figure 9. One year survival following experimental infarction in a rat model. Therapy groups: H_2O = placebo therapy (open bars); Cap = captopril therapy (solid bars) (Reference #102).

Pfeffer et al subsequently studied the effects of captopril therapy, commenced on day 14, on 1 year survival, in a placebo-controlled study of 302 rats with myocardial infarction (100-102). As expected, survival was directly related to infarct size in the placebo treated rats. However, treatment with the angiotensin converting enzyme inhibitor significantly ($p<0.02$) improved survival in the total group (Figure 9). The beneficial effect was most marked in those with moderate sized infarcts. The improvement in survival also appeared to be related to the attenuation of ventricular dilatation.

Pfeffer et al have also performed a pilot study in 59 patients with first, anterior, transmural myocardial infarctions, left ventricular ejection fractions of 45 percent or less, and no overt heart failure, to assess the efficacy of prophylactic treatment with an angiotensin converting enzyme inhibitor (103-104). Patients underwent cardiac catheterization on approximately day 18 post-infarction and were randomly assigned to captopril or placebo treatment for 1 year. At this time, there was a significant decrease in left ventricular end-diastolic pressure ($p<0.005$), pulmonary capillary wedge pressure ($p<0.01$) and mean pulmonary artery pressure ($p=0.05$) compared to baseline in the captopril-treated but not the placebo-treated patients. Conversely, left ventricular end-diastolic volume increased significantly ($p<0.02$) in the placebo-treated but not the captopril-treated patients. However, the intergroup analyses for each of these variables did not achieve statistical significance. In this study, the two most important predictors of ventricular dilatation were (1) persistent occlusion of the infarct-related artery at baseline catheterization and (2) the extent of wall motion abnormality, defined as akinesis plus dyskinesis of 30% or more of the diastolic perimeter at baseline. The greatest benefit of treatment with the angiotensin converting enzyme inhibitor was seen in those with a closed infarct-related artery and akinesis + dyskinesis involving more than 30% of the perimeter of the left ventricle (Figure 10). It is worth noting that more than 50% of the patients in each group were also receiving beta-blocker therapy. A recent study from Sharpe et al (105) in 60 patients following acute myocardial infarction supports the observation that treatment with an angiotensin converting enzyme inhibitor may have a beneficial effect on left ventricular dilatation and remodelling.

Although the results observed, both in animal models and in man, suggest a potentially beneficial effect of treatment with angiotensin-converting enzyme inhibitor therapy, in the prevention of left ventricular dilatation, such data should be regarded as preliminary until results from the larger ongoing multicenter SAVE and SOLVD studies (106) become available.

Although it is conceivable that angiotensin converting enzyme inhibitors may possess unique properties that result in an attenuation in left ventricular dilatation (for example related to abolition of the "toxic" effects of angiotensin II on the myocardium or effects on G_s), it seems more likely that their effects are related to a reduction in systolic and diastolic wall stress, without an accompanying reflex increase in catecholamines, during the period of remodelling. It also seems intuitively likely, although unproven that earlier intervention with such agents, aimed at limiting infarct size and reducing wall tension as soon as

possible post-infarction, may have an even more salutary effect on left ventricular dilatation than when treatment is commenced only days to weeks post-infarction. Further studies will be necessary to answer these questions definitively, and to determine the potential incremental benefit of such therapy when used in conjunction with thrombolytic therapy or emergency angioplasty for acute myocardial infarction.

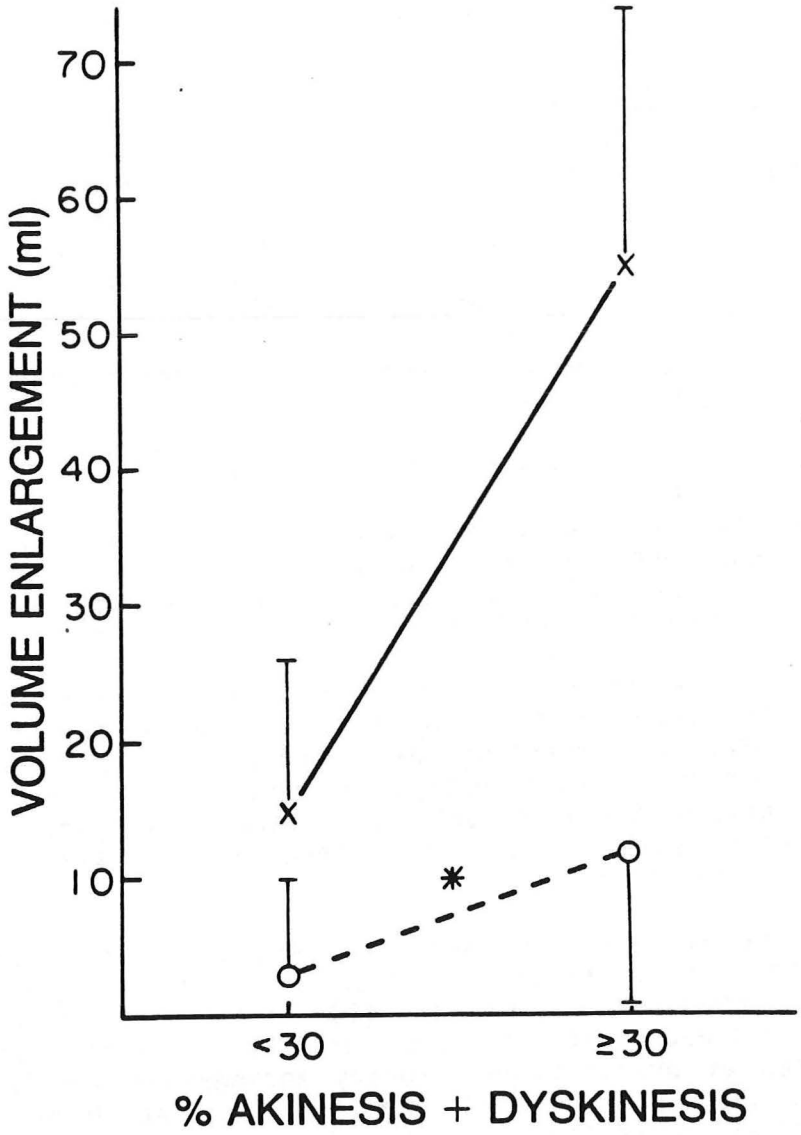


Figure 10. Increase in left ventricular end-diastolic volume from baseline (volume enlargement) in patients with occlusion of the left anterior descending coronary artery at baseline catheterization (n=36) (Reference #104).

D. Patency of the Infarct Related Artery and LV Dilatation

The advent of thrombolytic therapy (and/or acute coronary angioplasty) for myocardial infarction, as well as the observations in the study by Pfeffer et al (104) in man, raise the question of the possible

role that infarct-related artery patency may play in preventing or ameliorating left ventricular dilatation. McKay et al performed coronary angiography and left ventriculography within the first few hours of infarction, and again at 14 days, in 30 patients who received thrombolytic therapy (107). Patients included in this report were only those who showed both an early and a late improvement of flow in the infarct-related artery. Despite this, there was a significant increase ($p<0.01$) in left ventricular end-systolic and end-diastole volume indices in the group as a whole by two weeks. The increase in left ventricular end-diastolic volume index correlated directly ($r=0.71$, $p<0.001$) with the percentage of the ventriculographic silhouette that was akinetic or dyskinetic at the initial catheterization i.e. the infarct size. There was a mean increase of 13% in the endocardial perimeter length of infarcted segments and 19% in the noninfarcted segments. At the same time, there was a decrease in left ventricular filling pressures and an increase in cardiac output, that occurred at the expense of a significant increase in ventricular chamber volumes. *Thus, this study confirms the observation that left ventricular dilatation occurs to a similar or greater degree in the noninfarcted myocardium as in the infarcted region* and suggests that a persistently patent infarct related artery *per se* does not prevent the occurrence of left ventricular dilatation. However, it does not exclude the possibility that the degree of dilatation might have been greater if the infarct related artery were not patent, nor that these observations may in part be due to suboptimal restoration of blood flow due to a significant residual stenosis. These investigators (108) also studied the time course of left ventricular dilatation after acute transmural myocardial infarction in man with serial radionuclide ventriculograms performed on day 1, day 11 and after 10.6 months, in 36 patients. Twenty of the 36 showed more than 20% increase in left ventricular volume. Left ventricular dilatation was more frequent and chronic dilatation significantly more marked ($p<0.01$) in those with left anterior descending as opposed to right coronary artery occlusion. However, these investigators could not discern a difference in outcome, in terms of the left ventricular volumes or ejection fraction, for those patients with succcessful thrombolysis versus unsuccessful thrombolysis at 5 ± 1 hour.

Jeremy et al also addressed the question of the effect of infarct artery patency on subsequent ventricular volume changes, and came to diametrically opposite conclusions (109-111). In their study of 40 patients who did not receive thrombolytic therapy, infarct artery perfusion was documented at predischarge coronary angiography and left ventricular volumes were measured within 48 hours and at 1 month following a first acute myocardial infarction. By multiple linear regression analysis, the degree of perfusion of the infarct artery ($r=0.58$, $p=0.001$) was a more important predictor of volume change than was infarct size measured by peak creatine kinase ($r=0.30$, $p=0.009$). Left ventricular dilatation ($\geq$20% increase in volume) occurred in all 14 patients without perfusion of the infarct-related artery, compared with only 2 of 26 patients with perfusion of this artery, due to subtotal occlusion or collateral vessels ($p<0.001$).

The results of the ISIS-2 trial, a placebo-controlled trial (112) of streptokinase, aspirin, or the combination, in over 17,000 patients with acute myocardial infarction also raise the possibility that thrombolytic agents may improve survival by mechanisms unrelated to acute salvage of

myocardium. In this study, a beneficial effect on survival was seen in the patients treated up to 24 hours after the onset of chest pain. It seems at least possible that late patency of the infarct-related artery induced by thrombolytic therapy might have played a role in this improvement in survival. At present, the importance of infarct-related artery perfusion, the time at which this needs to be present in order to limit left ventricular dilatation, and the mechanism(s) whereby it may limit ventricular dilatation, are unresolved and under active investigation (113,114).

X. SUMMARY

Left ventricular dilatation and remodelling occurs in 35-40% of anterior transmural myocardial infarcts, and is an important antecedent factor to the development of late congestive heart failure. This process commences within the first 24 hours and may be steadily progressive over months to years. Both the infarcted and the uninfarcted region of the myocardium are equally involved in the process. Thinning of the left ventricular wall occurs mainly as a result of cell slippage. In addition, compensatory hypertrophy occurs in the uninfarcted segment of the myocardium. While this hypertrophy may initially be physiological, it ultimately appears to become a pathological process and thereby contributes to the pump dysfunction. At the present time there are encouraging data to suggest that nitroglycerin, administered in the setting of the acute infarction, or the angiotensin converting enzyme inhibitor captopril, may ameliorate this process. Whether a patent infarct related artery further serves to limit dilatation is uncertain and is currently under investigation.

ACKNOWLEDGMENTS

I should like to acknowledge the expert secretarial assistance of Mrs. Belinda Lambert and the invaluable contribution made by Dr. Preston Dunnmon to the formulation of these Grand Rounds.

REFERENCES

1. Yancy CW Jr, Firth BG: Congestive heart failure. *Disease-a-Month* 34:467-536, 1988.
2. Kannel WB, Sorlie P, McNamara PM: Prognosis after initial myocardial infarction. The Framingham Study. *Am J Cardiol* 44:53-59, 1979.
3. 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* 5:831-836, 1983.
4. Furberg CD, Yusuf S: Effect of vasodilators on survival in chronic congestive heart failure. *Am J Cardiol* 55:1110-1113, 1985.
5. McKee PA, Castelli WP, McNamara PM, Kannel WB: The natural history of congestive heart failure: The Framingham Study. *N Engl J Med* 285:1441-1446, 1971.
6. McFate Smith W: Epidemiology of congestive heart failure. *Am J Cardiol* 55:3A-8A, 1985.
7. Schlant RC, Sonnenblick EH: Pathophysiology of heart failure, in Hurst J, eds: *The Heart* (6th Ed). McGraw-Hill Book Co., New York, 1986, pp 319-345.
8. Lipid Research Clinics Program: The Lipid Research Clinics coronary primary prevention trial results. I. Reduction in incidence of coronary heart disease. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 251:351-374, 1984.
9. Serruys PW, Simoons ML, Suryapranata H, et al: Preservation of global and regional left ventricular function after early thrombolysis in acute myocardial infarction. *J Am Coll Cardiol* 7:729-742, 1986.
10. Hammermeister KE, De Rouen TA, Dodge HT: Variables predictive of survival in patients with coronary disease. *Circulation* 59:421-430, 1979.
11. White HD, Norris RM, Brown MA, Brandt PWT, Whitlock RML, Wild CJ: Left ventricular end-systolic volume as the major determinant of survival after recovery from myocardial infarction. *Circulation* 76:44-51, 1987.
12. Klein MD, Herman MV, Gorlin R: A hemodynamic study of left ventricular aneurysm. *Circulation* 35:614-630, 1967.
13. Kitamura S, Kay JH, Krohn BG, Magidson O, Dunne EF: Geometric and functional abnormalities of the left ventricle with a chronic, localized, non-contractile area. *Am J Cardiol* 31:701-707, 1973.
14. Hutchins GM, Bulkley BH: Infarct expansion versus extension: Two different complications of acute myocardial infarction. *Am J Cardiol* 41:1127-1132, 1978.
15. Eaton LW, Weiss JL, Bulkley BH, Garrison JB, Weisfeldt ML: Regional cardiac dilatation after acute myocardial infarction: Recognition by two-dimensional echocardiography. *N Engl J Med* 300:57-62, 1979.
16. Erlebacher JA, Weiss JL, Eaton LW, Kallman C, Weisfeldt ML, Bulkley BH: Late effects of acute infarct dilation on heart size: A two-dimensional echocardiographic study. *Am J Cardiol* 49:1120-1126, 1982.
17. Meizlisch JL, Berger HJ, Plankey M, et al: Functional left ventricular aneurysm formation after acute transmural myocardial

infarction: Incidence, natural history, and prognostic implications. *N Engl J Med* 311:1001-1006, 1984.

18. Mann DL, Foale RA, Gillam LD, Schoenfeld D, Newell J, Weyman AE: Early natural history of regional left ventricular dysfunction after experimental myocardial infarction. *Am Heart J* 115:538-546, 1988.
19. Weisman HF, Healy B: Myocardial infarct expansion, infarct extension, and reinfarction: Pathophysiologic concepts. *Progress in Cardiovasc Dis* 30:73-110, 1987.
20. Eaton LW, Bulkley BH: Expansion of acute myocardial infarction: Its relationship to infarct morphology in a canine model. *Circ Res* 49:80-88, 1981.
21. Weisman HF, Bush DE, Mannisi JA, Bulkley BH: Global cardiac remodeling after acute myocardial infarction: A study in the rat model. *J Am Coll Cardiol* 5:1355-1362, 1985.
22. Nolan SE, Mannisi JA, Bush DE, Healy B, Weisman HF: Increased afterload aggravates infarct expansion after acute myocardial infarction. *J Am Coll Cardiol* 12:1318-1325, 1988.
23. Pierard LA, Albert A, Gilis F, Sprynger M, Carlier J, Kulbertus HE: Hemodynamic profile of patients with acute myocardial infarction at risk of infarct expansion. *Am J Cardiol* 60:5-9, 1987.
24. Christensen DJ, Ford M, Reading J, Castle CH: Effect of hypertension on myocardial rupture after acute myocardial infarction. *Chest* 72:618-622, 1977.
25. Hammerman H, Schoen FJ, Braunwald E, Kloner RA: Drug-induced expansion of infarct: morphologic and functional correlations. *Circulation* 69:611-617, 1984.
26. Hammerman H, Kloner RA, Hale S, Schoen FJ, Braunwald E: Dose-dependent effects of short-term methylprednisolone on myocardial infarct extent, scar formation, and ventricular function. *Circulation* 68:446-452, 1983.
27. Mannisi JA, Weisman HF, Bush DE, et al: Steroid administration after myocardial infarction promotes early infarct expansion: A study in the rat model. *J Clin Invest* 79:1431-1439, 1987.
28. Cohn JN: Current therapy of the failing heart. *Circulation* 78:1099-1107, 1988.
29. Weisman HF, Bush DE, Mannisi JA, Weisfeldt ML, Healy B: Cellular mechanisms of myocardial infarct expansion. *Circulation* 78:186-201, 1988.
30. Rubin SA, Fishbein MC, Swan HJC: Compensatory hypertrophy in the heart after myocardial infarction in the rat. *J Am Coll Cardiol* 1:1435-1441, 1983.
31. Anversa P, Loud AV, Levicky V, Guideri G: Left ventricular failure induced by myocardial infarction. I. Myocyte hypertrophy. *Am J Physiol* 248:H876-882, 1985.
32. Anversa P, Beghi C, Kikkawa Y, Olivetti G: Myocardial response to infarction in the rat: morphometric measurement of infarct size and myocyte cellular hypertrophy. *Am J Pathol* 118:484-492, 1985.
33. Bishop S: Ultrastructure of the myocardium in physiologic and pathologic hypertrophy in experimental animals, in Alpert NR, eds: *Perspectives in Cardiovascular Research*. Raven Press, New York, 1983, pp. 127-147.
34. Wikman-Coffelt J, Parmley WW, Mason DT: The cardiac hypertrophy process: Analyses of factors determining pathological vs physiological development. *Circ Res* 45:697-707, 1979.

35. Scheuer J, Bhan AK: Brief Reviews: Cardiac contractile proteins: Adenosine triphosphate activity and physiological function. *Circ Res* 45:1-12, 1979.
36. Bishop SP, Drummond JL: Cell size and surface morphology of isolated cardiac myocytes from normally growing rats. *Fed Proc* 37:229, 1978 (Abstract).
37. Holtz J, Restarff WV, Bard P, Bassenge E: Transmyocardial distribution of myocardial blood flow and of coronary reserve in canine left ventricular hypertrophy. *Basic Res Cardiol* 72:286-292, 1977.
38. Page E, Earley J, Power B: Normal growth of ultrastructure in rat left ventricular myocardial cells. *Circ Res* 34-35:(Suppl II)-12-16, 1974.
39. Anversa P, Loud AV, Vitali-Mazza L: Morphometry and autoradiography of early hypertrophic changes in the ventricular myocardium of adult rat. An electron microscopic study. *Lab Invest* 35:475-483, 1976.
40. Meerson FZ, Zaletayeva TA, Lagutchev SS, Pshennikova MG: Structure and mass of mitochondria in the process of compensatory hyperfunction and hypertrophy of the heart. *Exp Cell Res* 36:568-578, 1964.
41. Meerson FZ: The myocardium in hyperfunction, hypertrophy and heart failure. *Circ Res* 25:(Suppl II)-1-163, 1969.
42. Anversa P, Loud AV, Giacomelli F, Weiner J: Absolute morphometric study of myocardial hypertrophy in experimental hypertension. II: Ultrastructure of myocytes and interstitium. *Lab Invest* 38:597-609, 1978.
43. Page E, Polimeni PI, Zak R, Earley J, Johnson M: Myofibrillar mass in rat and rabbit heart muscle: Correlation of microchemical and stereological measurements in normal and hypertrophied hearts. *Circ Res* 30:430-439, 1972.
44. Rakusan K, Moravec J, Hatt PY: Regional capillary supply in the normal and hypertrophied rat heart. *Microvasc Res* 20:319-326, 1980.
45. Shipley RA, Shipley LJ, Wearn JT: The capillary supply in normal and hypertrophied hearts of rabbits. *J Exp Med* 65:29-44, 1936.
46. Caulfield JB: Morphologic alterations of the collagen matrix with cardiac hypertrophy, in Alpert NR, eds: *Perspectives in Cardiovascular Research: Myocardial hypertrophy and failure*, Raven Press, New York, 1983, pp. 167-175.
47. Weber KT, Janicki JS, Pick R, et al: Collagen in the hypertrophied, pressure-overloaded myocardium. *Circulation* 75:(Suppl I)-40-47, 1987.
48. Murray PA, Vatner SF: Reduction of maximal coronary vasodilator capacity in conscious dogs with severe right ventricular hypertrophy. *Circ Res* 48:25-33, 1981.
49. Bertrand ME, Lablanche JM, Tilmant PY, Thieleux FP, Delforge MR, Carre AG: Coronary sinus blood flow at rest and during isometric exercise in patients with aortic valve disease: Mechanism of angina pectoris in presence of normal coronary arteries. *Am J Cardiol* 47:199-205, 1981.
50. Nitenberg A, Foult JM, Blanchet F, Zouioueche S: Multifactorial determinants of reduced coronary flow reserve after dipyridamole in dilated cardiomyopathy. *Am J Cardiol* 55:748-754, 1985.
51. Karam R, Wicker P, Sen S, Healy B: Coronary circulation in post-infarction cardiac hypertrophy. *Circulation* 78:(Suppl II)-170, 1988 (Abstract).

52. Katz AM: The myocardium in congestive heart failure. Am J Cardiol 63:12A-16A, 1989.
53. 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 12:781-795, 1980.
54. Page E, McAllister LP: Quantitative electron microscopic description of heart muscle cells. Application to normal, hypertrophied and thyroxine-stimulated hearts. *Am J Cardiol* 31:172-181, 1973.
55. Furchgott RF, Lee KS: High energy phosphates and the force of contraction of cardiac muscle. *Circulation* 24:416-432, 1961.
56. Pool PE, Spann JF Jr, Buccino RA, Sonnenblick EH, Braunwald E: Myocardial high energy phosphate stores in cardiac hypertrophy and heart failure. *Circ Res* 21:365-373, 1967.
57. Bashore TM, Magorien DJ, Letterio J, Shaffer P, Waverferth DV: Histologic and biochemical correlates of left ventricular chamber dynamics in man. *J Am Coll Cardiol* 9:734-742, 1987.
58. Morgan HE, Gordon EE, Kira Y, Siehl DL, Watson PA, Chua BHL: Biochemical correlates of myocardial hypertrophy. *The Physiologist* 28:18-27, 1985.
59. Morgan HE, Chua BHL, Siehl D, Kira Y, Kochel PJ, Gordon HE: Mechanical factors affecting protein turnover in isolated rabbit hearts. *Federation Proc* 45:2563-2567, 1986.
60. Alpert N: Cellular and subcellular basis of myocardial hypertrophy. *Federation Proc* 45:2561-2567, 1986.
61. Hoh JFY, McGrath PA, Hale PT: Electrophoretic analysis of multiple forms of cardiac myosin: effect of hypophysectomy and thyroxine replacement. *J Mol Cell Cardiol* 10:1053-1076, 1978.
62. Everett AW, Umeda PK, Sinha AM, Rabinowitz M, Zak R: Expression of myosin heavy chains during thyroid hormone-induced cardiac growth. *Federation Proc* 45:2568-2572, 1986.
63. Umeda PK, Darling DS, Kennedy JM, Jakovcic S, Zak R: Control of myosin heavy chain expression in cardiac hypertrophy. *Am J Cardiol* 59:49A-55A, 1987.
64. Rappaport L, Swynghedauw B, Mercadier JJ: Physiologic adaptation of the heart to pathological overloading. *Federation Proc* 45:2573-2579, 1986.
65. Schwartz K, Lecarpentier Y, Martin JL, Lompre AM, Mercadier JJ, Swynghedauw B: Myosin isoenzymic distribution correlates with speed of myocardial contraction. *J Mol Cell Cardiol* 13:1071-1075, 1981.
66. Mercadier JJ, Bouveret P, Gorza L, et al: Myosin isoenzymes in normal and hypertrophied human ventricular myocardium. *Circ Res* 53:52-62, 1983.
67. Re RN: Cellular biology of the renin-angiotensin systems. *Arch Intern Med* 144:2037-2047, 1984.
68. Dzau VJ, Re RN: Evidence of the existence of renin in the heart. *Circulation* 75:(Suppl I)-134-136, 1987.
69. Dzau VJ: Implications of local angiotensin production in cardiovascular physiology and pharmacology. Am J Cardiol 59:59A-65A, 1987.
70. Bristow MR, Kantrowitz NE, Ginsburg R, Fowler MB: Beta-adrenergic function in heart muscle disease and heart failure. J Mol Cell Cardiol 17:(Suppl 2)-41-52, 1985.

71. Rodbell M, Lad PM, Nielsen TB, et al: The structure of adenylate cyclase systems. *Adv Cyclic Nucleotide Res* 14:3-14, 1981.
72. Yatani A, Imoto Y, Codina J, Hamilton SL, Brown AM, Birnbaumer L: The stimulatory G protein of adenylyl cyclase, G_s, also stimulates dihydropyridine-sensitive Ca^{2+} channels. *J Biol Chem* 263:9887-9895, 1988.
73. Thomas JA, Marks BH: Plasma norepinephrine in congestive heart failure. *Am J Cardiol* 41:233-243, 1978.
74. Ginsburg R, Bristow MR, Billingham ME, Stinson EB, Schroeder JS, Harrison DC: Study of normal and failing isolated human hearts: Decreased response of failing heart to isoproterenol. *Am Heart J* 106:535-540, 1983.
75. Fowler MB, Laser JA, Hopkins GL, Minobe W, Bristow MR: Assessment of the beta-adrenergic receptor pathway in the intact failing human heart. Progressive receptor down-regulation and subsensitivity to agonist response. *Circulation* 74:1290-1302, 1986.
76. Vatner DE, Vatner SF, Fuji AM, Homcy CJ: Loss of high affinity cardiac beta-adrenergic receptors in dogs with heart failure. *J Clin Invest* 76:2259-2264, 1985.
77. Longabaugh JP, Vatner DE, Vatner SF, Homcy CJ: Decreased stimulatory guanosine triphosphate binding protein in dogs with pressure overload left ventricular failure. *J Clin Invest* 81:420-242, 1988.
78. Kessler PD, Cates AE, Van Dop C, Feldman AM: Decreased bioactivity of the guanine nucleotide-binding protein that stimulates adenylate cyclase in hearts from cardiomyopathic syrian hamsters. *J Clin Invest* 84:244-252, 1989.
79. Horn EM, Corwin SJ, Steinberg SF, et al: Reduced lymphocyte stimulatory guanine nucleotide regulatory protein and beta-adrenergic receptors in congestive heart failure and reversal with angiotensin converting enzyme inhibitor therapy. *Circulation* 78:1373-1379, 1988.
80. Ferrans VJ, Hibbs RG, Walsh JJ, Burch GE: Histochemical and electron microscopical studies on the cardiac necroses produced by sympathomimetic agents. *Ann NY Acad Sci* 156:309-332, 1969.
81. Lee HR, Henderson SA, Reynolds R, Dunnmon P, Yuan D, Chien KR: $Alpha_1$ adrenergic stimulation of cardiac gene transcription in neonatal rat myocardial cells: Effects on myosin light chain-2 gene expression. *J Biol Chem* 263:1-7, 1988.
82. Simpson P: Norepinephrine-stimulated hypertrophy of cultured rat myocardial cells is an $alpha_1$ adrenergic response. J Clin Invest 72:732-738, 1983.
83. Meidell RS, Sen A, Henderson SA, Slahetka MF, Chien KR: $Alpha_1$ adrenergic stimulation of rat myocardial cells increases protein synthesis. *Am J Physiol* 251:1076-1084, 1986.
84. Dunnmon PM, Henderson SA, Sen A, Reynolds R, Iwaki K, Chien KR: Phorbol esters induce the accumulation and assembly of myosin light chain-2 in purified neonatal rat myocardial cells. In press, 1989.
85. Dunnmon PM: Unpublished observations.
86. Breitbart RE, Adreadis A, Nadal-Ginard B: Alternative splicing: A ubiquitous mechanism for the generation of multiple protein isoforms from single genes. *Ann Rev Biochem* 56:467-495, 1987.
87. Jugdutt BI: Myocardial salvage by intravenous nitroglycerin in conscious dogs: Loss of beneficial effect with marked nitroglycerin-induced hypotension. *Circulation* 68:673-684, 1983.

88. Jugdutt BI: Delayed effects of early infarct-limiting therapies on healing after myocardial infarction. *Circulation* 72:907-914, 1985.
89. Jugdutt BI, Sussex BA, Warnica JW, Rossall RE: Persistent reduction in left ventricular asynergy in patients with acute myocardial infarction by intravenous nitroglycerin. *Circulation* 68:1264-1273, 1983.
90. Jugdutt BI, Amy RWM: Healing after myocardial infarction in the dog: Changes in infarct hydroxyproline and topography. *J Am Coll Cardiol* 7:91-102, 1986.
91. Jugdutt BI, Warnica JW: Intravenous nitroglycerin therapy to limit myocardial infarct size, expansion and complications: Effect of timing, dosage and infarct location. *Circulation* 78:906-919, 1988.
92. Flaherty JT, Becker LC, Bulkley BH, et al: A randomized prospective trial of intravenous nitroglycerin in patients with acute myocardial infarction. *Circulation* 68:576-588, 1983.
93. Jaffe AS, Geltman EM, Tiefenbrunn AJ, et al: Reduction of infarct size in patients with inferior infarction with intravenous glyceryl trinitrate. A randomized study. *Br Heart J* 49:452-460, 1983.
94. Yusuf S, MacMahon S, Collins R, Peto R: Effect of intravenous nitrates on mortality in acute myocardial infarction: An overview of the randomized trials. *Lancet* 1:1088-1091, 1988.
95. Flaherty JT, Becker LC, Weiss JL, et al: Results of a randomized, prospective trial of intraaortic balloon counterpulsation and intravenous nitroglycerin in patients with acute myocardial infarction. *J Am Coll Cardiol* 6:434-446, 1985.
96. Ertl G, Kloner RA, Alexander RW, Braunwald E: Limitation of experimental infarct size by an angiotensin converting enzyme inhibitor. *Circulation* 65:40-48, 1982.
97. Westlin W, Mullane K: Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radicals? *Circulation* 77:(Suppl I)-30-39, 1988.
98. Pfeffer JM, Pfeffer MA, Braunwald E: Influence of chronic captopril therapy on the infarcted left ventricle of the rat. *Circ Res* 57:84-95, 1985.
99. Fletcher PJ, Pfeffer JM, Pfeffer MA, and Braunwald E: Left ventricular diastolic pressure - volume relations in rats with healed myocardial infarction: Effects on systolic function. *Circ Res* 49:618-626, 1981.
100. Pfeffer JM, Pfeffer MA, Braunwald E: Hemodynamic benefits and prolonged survival with long-term captopril therapy in rats with myocardial infarction and heart failure. *Circulation* 75:(Suppl I)-149-155, 1987.
101. Pfeffer MA, Pfeffer JM, Steinberg C, Finn P: Survival after an experimental infarction: Beneficial effects of long-term therapy with captopril. *Circulation* 72:406-412, 1985.
102. Pfeffer MA, Pfeffer JM: Ventricular enlargement and reduced survival after myocardial infarction. *Circulation* 75:(Suppl IV)-93-97, 1987.
103. Lamas G, Pfeffer MA: Increased left ventricular volume following myocardial infarction in man. *Am Heart J* 111:30-35, 1986.
104. Pfeffer MA, Lamas GA, Vaughan DE, Parisi AF, Braunwald E: Effect of captopril on progessive ventricular dilatation after anterior myocardial infarction. *N Engl J Med* 319:80-86, 1988.

105. Sharpe N, Murphy J, Smith H, Hannan S: Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet* 1:255-259, 1988.
106. Gorlin R: Treatment of congestive heart failure: Where are we going? *Circulation* 75:(Suppl IV)-108-111, 1987.
107. McKay RG, Pfeffer MA, Pasternak RC, et al: Left ventricular remodeling after myocardial infarction: A corrolary to infarct expansion. *Circulation* 74:693-702, 1986.
108. Warren SE, Royal HD, Markis JE, Grossman W, McKay RG: Time course of left ventricular dilation after myocardial infarction: Influence of infarct-related artery and success of coronary thrombolysis. *J Am Coll Cardiol* 11:12-19, 1988.
109. Jeremy RW, Allman KC, Bautovitch G, Harris PJ: Patterns of left ventricular dilation during the six months after myocardial infarction. *J Am Coll Cardiol* 13:304-310, 1989.
110. Jeremy R, Bautovich G, Harris P: Patterns of left ventricular dilation and prognosis late after infarction. *Circulation* 78:II-502, 1988 (Abstract).
111. Jeremy RW, Hackworthy RA, Bautovitch G, Hutton BF, Harris PJ: Infarct artery perfusion and changes in left ventricular volume in the month after acute myocardial infarction. *J Am Coll Cardiol* 9:989-995, 1987.
112. ISIS 2 Collaborative Group: Randomized trial of intravenous streptokinae, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS 2. *Lancet* 2:349-360, 1988.
113. Valente M, Klugman S, Niccoli L, et al: Importance of early recanalization of the occluded coronary artery in acute myocardial infarction for preservation of left ventricular function. *J Mol Cell Cardiol* 20:(Suppl 2)-145-154, 1988.
114. Braunwald E: Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival. Should the paradigm be expanded? *Circulation* 79:441-444, 1989.