Cardiac Remodeling

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Paradigms of Heart Failure

Historically heart failure (HF) has been viewed using many syndrome models. One of the first useful models of HF was the cardio-renal model. Clinicians viewed HF predominantly as a problem of failure of the heart and kidneys to effectively process fluid. Low cardiac output led to poor renal perfusion, which led to excessive salt and water retention, and thus fluid overload. In this era, diuretics and digitalis were the predominant medications available.[1]

It became apparent that HF was significantly related to poor cardiac pump performance and low cardiac output. A second model of HF, the cardio-circulatory model, was introduced. This hemodynamic model of HF emphasized pressure measurements, characterization of the reduction of cardiac output and characterization of changes in systemic and pulmonary vascular resistance. In this era, new drugs introduced for HF included agents that had direct effects on cardiac output and also direct effects on both venous tone and arterial tone. These drugs, when combined with diuretics, allowed particularly effective treatment of acute exacerbations of HF with fluid overload and low output states. Patients frequently rapidly improved, leading to the concept that a patient was “in heart failure” or “out of heart failure.” Drugs tested at this time directly caused vasodilation or increased cardiac output by positive inotropic effects. As time progressed, it became apparent that while these agents resulted in short-term gain and ameliorated acute crises, long-term management of HF was fraught with problems. Mortality rates in long-term trials of positive inotropes appeared to increase and it gradually became apparent that the rate of progression of the disease process, rather than being slowed down, might actually have been sped up.[1]

As better imaging became available to characterize structural changes and a better understanding of molecular physiology of the myocyte and fibrocyte was obtained, HF has come to be viewed as a relentlessly progressive disorder. The first real understanding of the concept of remodeling came with the development of the neurohormonal model of heart failure. This model emphasized that chronic continuous stimulation of control systems originally designed to control moment-to-moment circulatory tone and responsiveness was maladaptive.[1] A large series of studies recognized that chronic stimulation of the renin-angiotensin-aldosterone system had many detrimental effects, not only salt retaining, hemodynamic, and vasoconstrictive, but also structural,

cellular, and molecular. The insight that inhibition of the over-stimulation of these systems resulted in a slowing of disease progression and an improvement in mortality was a significant achievement. Further recognition that chronic excessive stimulation of the adrenergic nervous system was also detrimental in a similar fashion, also leading to disease progression, further advanced the neurohormonal model. The neurohormonal model is the most effective model of HF developed and is the basis for much of our currently successful therapy with angiotensin converting enzyme inhibitors, angiotensin receptor blocking agents, beta blockers, and aldosterone antagonists.[2]

Recently, several investigators have emphasized the progressive nature of heart failure. As shown in Slides 2 and 3, heart failure can be viewed as occurring after an index event that causes an initial decline in output capacity of the heart.[2] If the decline is significant and the patient does not recover sufficiently from this incident event to restore normal cardiac output response, a series of systemic compensatory mechanisms become activated. In addition to traditional neurohormonal system activation, other factors (many perhaps in the local environment of the left ventricle) related to cytokines, endothelin, and other systems become activated to produce compensatory changes in the left ventricle. When these control systems are initially activated, the compensatory mechanisms recruited sometimes produce restoration of normal pump function. As a result, the activated control systems return to baseline levels of activation and a stable long-term outcome is the result. However, if restoration back to normal performance is not possible, the control systems remain continuously activated and progressive secondary damage of multiple components of the cardiovascular system occur. These secondary effects result in what has become to be known as remodeling of the heart and circulation. Continued progression of this process may result in a series of positive feedback loops that produce an inadequate compensation that only partially improves cardiac performance, which in turn causes a greater amount of stimulation that causes further and more severe damage (Slide 4). Ultimately, cardiac performance continues to decline over time, and if not intervened upon the patient suffers progressively more severe symptomatic heart failure and ultimately death (Slide 5).[2]

Cardiac Remodeling

Cardiac remodeling is defined as a condition induced by a cardiac injury. This cardiac injury may be a myocardial infarction (the most common cause in Western populations), a non-ischemic cardiomyopathy, end-stage valvular heart disease due typically to a regurgitant valve disorder, end-stage valve disease from chronic aortic stenosis, hypertensive heart disease, chronic anemia, or an infiltrating disease that caused a decrease in myocyte function. The degree of

remodeling is defined by the size, shape, and function changes that manifest themselves after injury. Remodeling invokes changes in genome expression, changes in molecular performance within the cell, changes in cellular shape and function, and changes in interstitial structures related to the fibrocyte. The degree of remodeling can be further enhanced by circulatory hemodynamic changes, chronic neurohormonal control system stimulation, changes in the conduction system of the heart, and secondary structural changes in the heart and circulation (Slides 6,7,8).[3]

The neurohormonal model of HF is shown in Slide 9. After initial injury to the heart and an initial decline in cardiac performance, wall stress on the myocytes increases, myocyte performance declines, and neurohormonal systems are activated. Simultaneously, this activation can cause any number of responses: peripheral vasoconstriction, hemodynamic changes in vascular tone, salt and water retention, and symptoms typical of HF, those being fatigue, shortness of breath, pulmonary congestion, and systemic fluid retention. As remodeling progresses, there may be continued worsening clinical symptoms. Other markers of compensatory activation besides increases in serum levels of the typical neurohormones (adrenergic tone, angiotensin II, and aldosterone) include increases in TNF-alpha, natriuretic peptides such as ANP and BNP, nitric oxide, and various cytokines. While increased levels of some of these substances may be viewed as beneficial, such as activation of natriuretic peptides and nitric oxide, the overall response of the circulatory system is quite inadequate to counterbalance the rather marked increases in the neurohormones.[2]

All of these compensatory activities appear to take place regardless of the initial type of cardiac injury. Thus, the HF phenotype defines a common set of responses; therefore, treatment for severe HF with significant remodeling emphasizes a common set of objectives.

Neurohormonal inhibitor therapy has been found to be highly effective treatment for patients with HF. Multiple trials of ACE inhibitors and beta-blockers have demonstrated reduction in total mortality, reduction in cardiac mortality, reduction in cardiovascular hospitalizations and hospitalizations for heart failure, reduction in symptoms of heart failure, and overall better quality of life. Despite the marked gains made by neurohormonal antagonism, it is still apparent that there is substantial cardiac morbidity and mortality in patients with HF. Therefore, neurohormonal therapy should be viewed as only being partially effective.

Several reasons have been explored for the potential lack of full efficacy and restoration of normal function by neurohormonal therapy. One theory suggests neurohormonal therapy itself is only able to effect a partial response, something that may initially be successful but ultimately is

unable to last for the long term in all patients. Thus, neurohormonal therapy serves as a reprieve, the rate of deterioration is attenuated, the rate of remodeling is slowed, but ultimately the process again begins, perhaps at a different pace. Clinically, few patients fully recover, but many partially improve. Is this simply a lack of full suppression of neurohormonal over-activation or are other, more complicated neurohormonal or yet undiscovered systems not suppressed by current therapy? Alternatively, are some parts of the neurohormonal system poorly accessed by current systemic therapy, particularly local paracrine systems in the heart?[2] It is unlikely that this theory fully explains the partial responses. Some trials that have more fully suppressed the renin angiotensin system, or particularly the sympathetic nervous system have ultimately been failures. They have either resulted in too many side effects or even harm. There appears to be a limit as to how vigorously the neurohormones can be suppressed before all circulatory reserve is lost.

A second theory suggests that neurohormonal therapy cannot fully explain all the issues related to HF and cardiac remodeling. Changes induced by cardiac remodeling, once in place, could be self sustaining. Thus, increases in wall stress, the shape changes induced by remodeling, the changes in structure at the cellular and molecular level, and other effects may be self sustaining and partially immune to neurohormonal control.[2] Let us further explore the potential mechanisms of cardiac remodeling.

The Cardiac Myocyte

Cardiac myocytes change shape and performance in response to different types of stimuli (Slides 10,11). A high output state or physiologic conditioning typically cause proportional growth of the myocyte, that is, the length of the myocyte increases and the diameter of the myocyte increases, but the proportion of lengths to diameters remains constant. This is physiologic growth. If the stimulus to this growth is removed, the myocyte will revert back toward a more normal size. These changes in myocyte size are similar to the changes that occur during normal growth from birth to adulthood.[4,5]

Pressure overload caused by such conditions as hypertension or aortic stenosis results initially in an increase in myocyte cross-sectional area. Thus the diameter of the myocyte grows disproportionately to length. New contractile units are put down in parallel to increase the maximum power output of the myocyte. Increasing diameter also helps reduce overall wall stress, decreasing afterload. Unrelenting, pressure overload continues to stimulate myocyte growth, but there is a limit. Ultimately the cell fails and dies if the stimulus is not removed.[4,5]

Volume overload states such as chronic valvular insufficiency, direct cardiomyopathies of a non-ischemic origin, or post-infarction remodeling of cells outside the infarct zone, involve a disproportionate increase in the length of the myocyte. In this situation, stretch receptors are activated and chamber wall thinning occurs as the myocyte becomes longer and leaner. As the myocytes thin and the walls thin, there is an increase in wall stress. Contractile units are put down in a series to effect this change in myocyte shape, but as with pressure overload, there is a limit to compensatory change. Without relief, the cell may die.[4,5]

The cytoskeleton of the myocyte helps maintain normal structural and mechanical integrity of the cell. Changes in loading conditions appear to be able to cause disruption of this homeostasis. Different types of loads cause different patterns of distortion, which may result in separate signaling pathways being activated that cause predominant change in length or predominant change in diameter of the myocyte. As a consequence of these stimuli, gene expression changes to help control the change in myocyte shape.[4,5]

The Fibroblast

The fibroblast is intimately related to maintaining structural integrity of the cardiac wall. Normal components of the fibrous skeleton of the heart are shown in Slide 12. Muscle bundles are formed by multiple myocytes. The myocytes are held together by a collagen weave and struts that forms the endomysium. Outside of these structures, groups of myocytes are bundled within the perimysium. These bundles are further grouped into larger units surrounded by more collagen fascia called epimysium.[6]

In HF, there is typically an abnormal proliferation of cardiac fibroblasts. Depending on the degree of proliferation of these fibroblasts, the laying down of increased fibrous tissue may accelerate the remodeling process of the heart. In some situations fibrosis is repairative, particularly following infarction or cell death in which a scar replaces normal myocytes. In other situations fibrosis is reactive and occurs remote from injury sites, and may be related to a more generalized stimulation of the cardiac fibrocyte. The amount of fibrous material within the heart and the amount of disorganization of the fibrous skeleton of the heart may also be proportional to the degree of stimulation of hypertrophy, particularly in pressure overload. Large amounts of fibrosis, particularly replacement fibrosis, may ultimately result in electrical isolation of some cells, which may provoke an increased propensity to arrhythmias. Other cells may be partially isolated but also distorted, so that overall functional performance of the myocyte is reduced and attenuated

because of loss of normal cellular integrity. There also appears to be an increase in the ratio of type I and type III collagen fibers (Slide 13).[7]

Apoptosis

Another cause of direct myocyte loss appears to be due to apoptosis. The importance of this mechanism that helps program cell death is not entirely clear. Several estimates have been made as to the rate of cell loss on an annual basis. These estimates range widely from very small percentages to potentially large percentages that are almost beyond belief. It appears clear that the rate of apoptosis does increase in patients with failing hearts as opposed to patients with still normal hearts. Thus, apoptosis may be part of the structural changes that occur and the physiologic response to increased loading conditions seen in heart failure.[2]

Changes in Chamber Shape and Function

Changes at the cellular level are translated to the chamber level and manifest as changes in structure of the heart, shape of the heart, and function of the heart.

Ischemic Disease

When the cause of remodeling is an acute myocardial infarction, particularly when it is a larger infarct in the anterior wall, the heart goes through a typical series of changes. The initial remodeling phase, early after the infarction, is focused on repair of the necrotic site. Replacement fibrosis and scar formation take over for necrotic myocytes. This change is beneficial and helps maintain cardiac function, and in smaller infarcts also helps maintain normal cardiac structure and shape. In larger infarcts, this initial shape change may also result in some slippage at the site of the scar and overall spherical enlargement and change in shape of the ventricle (Slide 14). Outside of the infarct zone, there is increased wall stress, and stimuli to hypertrophy occur from activation of stretch receptors and other neurohormonal changes. This generally results in disproportionate elongation and thinning of the myocytes as the stretch-induced load is applied. Over time the myocytes outside of the infarct zone may substantially decline in overall functional capacity, particularly following a large myocardial infarction. A late result after a large infarct is replacement fibrosis at the site of the initial necrotic event, evolution into a more spherically-shaped structure, or in some cases an aneurysmal-shaped structure and a decline in intrinsic function of myocytes outside the infarct zone with unfavorable loading conditions also accelerating the process in the areas outside of the infarct zone. Persistent elevations in wall stress in myocytes that are not involved in the infarct may continue to perpetuate further compensatory changes. This is part of the process that helps sustain and progress remodeling. As the process

goes on, geometry continues to evolve into a more spherical shape and the mitral valve apparatus may become progressively more stretched. This causes a reduction in motion of the leaflet structures in the long axis, an increase in annular diameter in the short axis, and ultimately enough stretch to reduce coaptation to the point that regurgitation begins to occur (Slides 15,16). Mitral regurgitation itself further increases the load on the heart by increasing preload and reducing overall forward stroke volume. This process may further enhance neurohormonal stimulation, toward even more remodeling. As this process continues, efficiency and oxygen utilization decline further and high wall stress may actually result in decreased perfusion of remaining myocytes, contributing even further to a reduction in overall systolic function.[2,3,8,9]

Fibroblasts may also respond to this increased angiotensin stimulation with further amounts of collagen synthesis and a switch in the ratio of type I to type III collagen. Aldosterone receptors within the heart may also participate in this process with increased amounts of aldosterone further stimulating hypertrophy and fibrosis.[6]

Desensitization of the beta receptor system and a shift in ratio of beta-1 to beta-2 subtypes is also frequently observed. As a result, myocytes become less responsive to typical beta-adrenergic signaling, which in some respects may be a protective effect since neurohormonal stimulation is constant. However, this attenuation of the signaling response also results in reduced cardiac output response to normal stimulation and which probably contributes to part of the clinical syndrome of HF. Examination of contractile performance of failing myocytes taken outside of infarct zones shows a substantial decline in contractility. There is also a decline in the response of the force-frequency ratio that normally increases contractility as heart rate increases.[2,8,10]

Non-ischemic pathways

The size and shape of the ventricle after non-ischemic injury takes a somewhat different pathway but ultimately results in a similar type of dilated cardiomyopathy. Non-ischemic cardiomyopathies tend to be more global in nature. The overall shape changes of the ventricle tend to be more equally distributed than in patients who have a discrete infarct scar or aneurysm formed. These ventricles (Slide 17) tend to gradually assume a more spherical and equally rounded shape as the disease process progresses. Changes throughout the left ventricle, as noted above in the discussion of changes in myocytes and fibrocytes outside of the infarct zone, appear to be relatively similar. There are areas of varying severity of fibrosis that occur. There also appears to be apoptosis detectable in non-ischemic hearts.

Patients that undergo heart failure as a direct consequence of pressure overload evolve through a different path. The initial response to the pressure overload signal is increased wall thickness, retention of a small chamber size – sometimes the chamber volume even decreases initially, and an increase in calculated mass (Slide 12). Associated with these changes are generally also changes in fibrosis. Ultimately, as the pressure overload disease continues to move forward, myocytes may eventually begin to elongate, allowing chamber dilation to occur. The heart may gradually evolve then from a small thick-walled chamber with preserved systolic performance into a gradually larger and still somewhat thick-walled chamber, with first significantly elevated filling pressures but preserved systolic performance followed later by a decline in systolic performance as ventricular size continues to rise. Typically, ventricles of this nature will always maintain a somewhat greater degree of wall thickness and in many cases a somewhat lesser amount of chamber enlargement. Ultimately, systolic performance declines to very low levels typical of other types of remodeled cardiac chambers.[4,11]

Clinical indicators of ventricular remodeling

It is very difficult by routine assessment of symptomatic status in patients with heart failure, categorization of exercise functional capacity, or physical exam to determine the degree of remodeling present in the heart. There is a dramatic variation in symptomatic limitation among individuals who have similar degrees of loss of systolic performance and shape change of the ventricle. Indeed, there is very little correlation between calculations such as resting ejection fraction or ventricular size and exercise capacity or clinical class of symptomatic limitation. Therefore, it has been found that information about symptomatic status of the patient is actually additive to the information obtained about cardiac structure and remodeling. Thus a complete interrogation and examination of a patient with heart failure includes not only careful assessment of both cardiac structure and function and also symptomatic limitations and functional capacity.

Central to the role of defining the severity of ventricular remodeling are imaging techniques. Echocardiography is the single most widely used evaluation of patients with symptomatic heart failure. A comprehensive echocardiogram allows assessment of ventricular size, shape, systolic function, right ventricular function, secondary changes in valvular function such as mitral valve performance and regurgitation, hemodynamics, particularly estimates of filling characteristics and pressures on the left side of the heart and secondary pulmonary hypertension and elevation in central venous pressure on the right side of the heart. All of these pieces of information should be a part of a routine comprehensive echocardiogram. Radionuclide imaging can provide information about ejection fraction and to some degree volumes, but does not allow most of the other

information obtained from the routine comprehensive echocardiogram. A major problem with echocardiography is image quality, quantitative reliability, and variation from study to study. Unfortunately, echocardiographic laboratories vary widely in the quality of work that they produce. Quantitative techniques, because of the amount of variability and noise in echocardiographic images, are still relatively crude in their capacity. Echocardiographic data on ventricular size and function is still predominantly a semi-quantitative technique based upon visual observation of multiple views of the 2-dimensional echocardiogram and integration of dimension measurements from M-mode or diameter measurements directly done on the 2-dimensional study. An experienced clinical echocardiographer is frequently more reliable in estimating size and function of the ventricles than a less experienced individual attempting 2-dimensional quantification. As echocardiographic techniques progress, more sophisticated tissue Doppler based measurements to assess synchrony and also muscle function may help improve quantitative reliability. Furthermore, 3-dimensional reconstruction now possible in many systems in near real time also has the potential to add reliability to calculations of volume, function, and mass.[12]

Cardiac magnetic resonance holds considerable promise because it clearly has substantially greater accuracy and thus potential reliability for serial calculation of ventricular size, function, and mass. However, the MRI remains a more time consuming and difficult to perform study, which is considerably less readily available and also considerably more expensive. Limitations yet to be overcome are problems with placing patients who have devices within the magnet. As device use becomes progressively more prevalent, this is a larger and larger minority of patients.

From cardiac imaging, the most effective data to help gauge remodeling is an assessment of left ventricular size. The degree of enlargement and the degree of shape change of the ventricle help define the amount of remodeling that has occurred. Prognostic information that has been found to be important is based upon end diastolic volumes, end systolic volumes, mitral valve regurgitation, and ventricular filling.[13] In many respects, the prognostic variables entered into a data set determine the “outcome predictors,” and all trials do not test the same echo variables. One of the most comprehensive trials to date was a substudy of BEST and the most powerful echocardiographic predictors of prognosis are shown in Slide 18.[13] Much more easily obtainable and more commonly evaluated in virtually all patients is left ventricular ejection fraction. Ejection fraction is clearly related to the degree of remodeling and tends to fall proportionally as overall ventricular size increases and function declines. It is also dependent on loading conditions. Outcomes analysis based upon ejection fraction have shown this to be a powerful prognostic

indicator for patients in HF and it is the most commonly used imaging data for evaluating patients with HF. Ejection fraction has become a key indicator to help guide therapy for both initiation of medications and also initiation and placement of devices. Changes in ejection fraction over time are also of prognostic import. Thus, the response to therapeutic intervention can be defined not only by symptoms but also by serial evaluation of ventricular volumes, dimensions, ejection fraction, mitral valve function, and ventricular filling patterns. Concordant improvement in symptoms with an increase in ejection fraction and a reduction in ventricular size are the most favorable indicators.[14]

A newer form of data comes from serum markers. Some studies have shown that there is a release of cardiac troponins with myocyte injury, not only when myocardial infarctions occur but also when patients have chronic HF. Persistent low-grade increases in troponin levels are potential markers for ongoing remodeling and deterioration.[15]

B-type natriuretic peptide released as part of the response to stretch receptor stimulation is also a powerful marker of prognosis. Multiple studies have been performed that show that the level of BNP achieved after initiation of therapy can indicate overall prognosis (Slide 19). In general, the lower BNP gets after therapeutic intervention, the better is the overall patient prognosis. Patients who have persistent high levels of BNP maintain markedly worse long-term prognosis. The findings of BNP, however, are still widely variable. It is difficult to use BNP in a more exact sense to guide therapy or detect changes in therapy unless baseline BNP data is available when the patient is hemodynamically optimized and very large shifts in BNP levels occur. Future refinements in the understanding of how BNP changes with acute exacerbations of heart failure may help increase the power of this measurement to guide interventions.[16]

Therapy

The new heart failure guidelines divide patients into four stages of heart failure (Slides 20,21). In Stage A patients are essentially at risk for developing heart failure. They do not yet have any structural changes in the heart nor do they have any symptomatic limitations. Thus, by definition, Stage A patients have no evidence of remodeling. The primary hallmark of therapy of Stage A patients is prevention. Thus, early intervention to prevent the development of coronary artery disease, to control hypertension and prevent the onset of hypertensive heart disease, to evaluate and intervene at the appropriate time in patients with developing valvular heart disease, or to monitor carefully patients with genetic predisposition to non-ischemic cardiomyopathies is of paramount importance. Also, controlling other risk factors, predominantly those that may lead to

premature coronary artery disease such as abnormal lipids, diabetes, and smoking, constitute the cornerstone of Stage A intervention.[12]

Stage B patients are those who have evidence of structural abnormality but no symptomatic limitation from heart failure. Thus, these patients by definition may have some degree of remodeling that may vary from minimal amounts, where cardiac function and size are near normal, to very substantial amounts in patients who have evolved in an asymptomatic fashion to a very large, remodeled, and reduced functioning heart. At this stage it is important to begin interventions that may attenuate the rate of remodeling, attenuate the rate of decline in ventricular function, or hopefully even reverse some of these changes. All of the therapies mentioned for Stage A are important for Stage B patients to minimize risk of progression. Other Stage B interventions of considerable importance are as follows: acute and effective intervention at the time of a myocardial infarction to limit infarct size, particularly in those who are at risk for a large myocardial infarction. High quality acute infarct care has been demonstrated to reduce infarct size and thus reduce the potential amount of remodeling that may occur. Also, studies have shown that opening the infarct-related artery, particularly in patients with large infarcts, may have a beneficial effect on preventing cardiac enlargement and remodeling over time even if this is after the infarct is complete. There appears to be an association of more remodeling and worsening long-term function in patients in which the infarct-related artery remains closed.[17,18]

The mainstay of Stage B therapy, however, is medical management. The most important Stage B interventions are institution of inhibitors of the renin-angiotensin-aldosterone system and institution of beta blockade to inhibit over-stimulation of the adrenergic nervous system. A large series of studies have evaluated the beneficial effects and shown conclusively (mainly in post infarct studies) the overall benefit of these therapies for preventing progression to a larger remodeled heart, reducing overall long-term mortality, and also reducing the likelihood of symptomatic shift from no clinical limitations with clinical HF. Examples of the mortality benefit of ACE inhibitors from these classic trials are show in Slides 22 and 23. In non-ischemic patients who are either minimally symptomatic or asymptomatic, the same types of therapy have been found to be beneficial. Thus, in patients in the SOLVD prevention trial and also in patients in the recently reported REVERT trial (Slide 24), both ACE inhibitors and beta blockers have been individually found to be of benefit. The CARMEN trial has shown that the combination of the two types of therapy is more powerful than one or the other alone (Slide 25). This has also been shown in retrospective analyses of the SAVE and SOLVD datasets (Slides 26,27). Therefore, even though patients are asymptomatic, in those who have reduced ejection fraction and increased

ventricular size, it is of significant importance to institute therapeutic doses of renin-angiotensin system inhibitors and beta blockers in this group of patients.[12,19,20]

Stage C patients correspond to traditional patients with heart failure. Stage C patients have both evidence of structural dysfunction of the heart and symptomatic limitation from clinical heart failure. A large number of trials have indicated the benefits of renin-angiotensin system inhibition in these patients. With regard to remodeling, inhibition of the renin-angiotensin system has a global beneficial effect on attenuating the rate of cardiac chamber enlargement. Inhibition of this system appears not to have a significant reversing effect on overall progression, but rather an attenuating effect (Slide 28). These findings have been best demonstrated in patients who have had large myocardial infarctions with ejection fractions typically 40% or less. Similar beneficial effects have been shown in non-ischemic dilated cardiomyopathies. The mechanism of benefit from ACE inhibitors is partially hemodynamic in that ACE inhibitors are balanced vasodilators causing pre-load reduction and also after-load reduction, and thus improve the hemodynamics of patients with ventricular dysfunction. Importantly, however, is that ACE inhibitors also have several effects at the cellular level. ACE inhibitors reduce stimuli for myocyte hypertrophy, reduce stimuli for fibrocyte hypertrophy, and thus reduce the propensity to develop greater amounts of fibrosis, and also have beneficial anti-remodeling effects on the structure of blood vessels. Further enhanced inhibition of the renin-angiotensin system occurs when aldosterone antagonists are added on top of ACE inhibitors. These agents appear to have additional clinical benefits in more severe heart failure patients or patients post myocardial infarction. Aldosterone antagonism appears to have a beneficial effect on reducing stimulation of cardiac fibroblasts, reducing the amount of fibrosis that occurs, and perhaps enhancing or helping reduce deterioration in the cardiac matrix around the myocytes (Slide 29).[12,19-22]

The use of angiotensin receptor blocking agents has been shown in multiple trials to be a substantially equivalent substitute for ACE inhibitors in patients who are ACE intolerant (Slide 30). Multiple studies have now shown non-inferiority and very good benefit clinically. There is also evidence of remodeling changes similar to those of ACE inhibitors (Slide 31). It has not been possible, however, to show definitive evidence that a combination of ACE inhibitors with angiotensin receptor blockers is highly beneficial. Some studies have demonstrated positive results of further reductions in morbidity and mortality and there is evidence of some increased anti-remodeling effects with combined therapy, but the overall results have been modest (slides 32,33).[23,24] It appears that a combination of aldosterone blockade with ACE inhibitors or

angiotensin receptor blockers may be a more powerful combination for mortality reduction than combined ACE inhibitor/angiotensin receptor blocker therapy.[12]

Beta blockers are now the second major cornerstone of therapy for patients with Stage C HF. Beta blockers were introduced later than ACE inhibitors for treatment of HF; thus, most beta blocker trials are trials added to coexisting therapy with diuretics, digoxin, and renin-angiotensin system inhibiting agents. Therefore, the beneficial effects seen in beta blocker trials (Slide 34) are those that show additional mortality reduction over standard baseline therapy. From a remodeling standpoint, beta blockers combined with renin-angiotensin inhibitors are the first medical therapy to show actual reversal of some of the remodeling effects. Patients who have a beneficial response to combined therapy typically have not only an improvement over time in ejection fraction but also a reduction in overall ventricular dimensions and volume. This effect typically is not a complete response but a partial response, particularly when patients have had longstanding heart failure. These beneficial findings occur in both non-ischemic and ischemic cardiomyopathies.[2,10,12]

The beneficial effects of beta blockers appear to come through several different mechanisms. Reduction in heart rate may have a favorable effect because of the abnormal force frequency response seen in patients with HF. A direct reduction in the continuous adrenergic stimulation of the myocardium also appears to reduce direct toxicity on the myocytes. There also may be a reduction in oxygen consumption and therefore a reduction in myocardial ischemia. Potential arrhythmias are also decreased by less adrenergic stimulation.[2,10] Beta blockers have also been shown to reverse some of the abnormal alterations in the biology of the myocyte.[25] Patients who have improved systolic performance, i.e. an improvement in ejection fraction, have been shown in analyses to have an increase in sarcoplasmic reticulum calcium ATP-ase mRNA and an improved ratio of alpha-myosin heavy chains to beta-myosin heavy chain RNA. These changes suggest a favorable impact on overall genomic expression within the myocyte, a reversion back to a more normal genomic expression profile. Thus, some pharmacotherapy now appears to show evidence of a direct impact on the molecular performance of the myocyte.[25]

Vasodilator therapy has generally been disappointing when the only effect is direct vasodilation. Agents such as calcium channel blockers, alpha blockers, and other direct vasodilators have been disappointing in that they have not had any overall beneficial effect. Indeed, use of unopposed vasodilators may stimulate the renin angiotensin system. Thus a simple increase in cardiac output due from vasodilation does not appear to have a salutary effect on long-term prognosis or remodeling. On the other hand, certain combinations of vasodilators such as the

combination of hydralazine and isosorbide dinitrate do appear to improve survival. In a recent trial of patients calling themselves African-Americans, there was an additive beneficial effect on top of standard therapy with renin-angiotensin system inhibition and beta blockers. The overall applicability of this type of additional therapy to other patient populations is uncertain at the present time.[26]

In select, carefully evaluated individuals with ischemic heart disease, there may be a substantial degree of myocardial hibernation. In these patients who manifest significant ischemia and poor perfusion, there may be a potential significant advantage to revascularization. Individual responses vary substantially and remain somewhat difficult to prove at present. However, an important aspect of full evaluation of patients with ischemic heart disease as a mediator of ventricular dysfunction is an assessment of the potential benefit of revascularization.[12,20]

Device Therapy

Mechanical devices are being progressively utilized to a much greater degree in patients with remodeled dysfunctional ventricles. Devices fall into three major categories, those being: 1) devices that resynchronize abnormal contractile stimulation of the left ventricle and potentially also abnormal dyssynchronous relaxation, 2) devices that inhibit the propensity of the heart to enlarge, these being predominantly passive devices placed somewhere within the ventricle or on the exterior surface of the ventricle, and 3) devices which augment the performance of the heart by placing a mechanical pump in series with the left ventricle. These pumps are typically reserved for very end-stage patients or patients bridging to cardiac transplantation.

Cardiac Resynchronization Therapy

It has been found after several investigations that simultaneous pacing of the left and right ventricles (bi-ventricular pacing) in patients who typically have a left bundle branch block conduction delay combined with a dilated cardiomyopathy is of considerable benefit.[27,28] Typically, initiation of cardiac resynchronization pacing may result in almost instantaneous improvement on stroke volume, cardiac output, and at times symptoms. This improvement in stroke volume potentially has a beneficial effect that may cause reduction in chronic stimulation of the neurohormonal control system because cardiac output is increased. If neurohormonal stimulation can be decreased and structural performance of the ventricle enhanced, a reduction in the stimulation to hypertrophy should occur. Indeed, reports from multiple randomized trials have shown substantial improvement over time in stroke volume and ejection fraction coupled with a reduction in ventricular size, a typical anti-remodeling effect (Slide 35). Analysis of these patients has shown that the greater the amount of dyssynchronous contraction before placement of the

pacemaker, the greater is the likelihood of improvement in performance and the greater the likelihood of an anti-remodeling effect. The amount of dyssynchrony in a dilated cardiomyopathy is difficult to assess and methods used to make this assessment are still under development. The initial concept that only patients who had an electrical conduction delay as manifested by either a left bundle branch block or intraventricular conduction delay of some type on the 12-lead electrocardiogram would benefit from bi-ventricular pacing has now been called into question.[27,28] The response rate to bi-ventricular pacing when only the electrocardiogram is used to identify patients is about 70%. This suggests that some patients who are bi-ventricularly paced will have no benefit. Perhaps these patients do not have substantial dyssynchrony even though they have abnormal conduction by electrocardiogram. Conversely, other patients who do not manifest a typical classic conduction delay may manifest evidence of dyssynchrony when more sophisticated analyses of dyssynchrony are made. These patients potentially could show improvement from bi-ventricular pacing. At present, there is no substantial consensus as to what other types of measurements should be made to identify dyssynchrony. However, several promising studies have been published. Analyses of up to 12 segments of the left ventricle with tissue Doppler velocity imaging, measuring the time of onset of peak systolic tissue velocity, the actual peak systolic tissue velocity, peak diastolic tissue velocity, and other parameters have been evaluated. At this time, the most effective measurement is a simple measurement of the time interval from the onset of the ECG QRS complex to peak systolic tissue velocity in multiple segments (Slide 36). Studies disagree as to how many segments need to be measured. Some studies would suggest that measuring perhaps only two or four basal segments in the lateral and posterior walls and comparing these to the septal and anteroseptal walls might be enough to identify patients who would benefit from bi-ventricular pacing. On the other hand, more comprehensive analyses of 12 segments of the heart, looking at all the walls at the basal and middle levels, offer considerable promise.[27,28]

Analysis of interventricular dyssynchrony, that is, delays between the left and right ventricle, have also been shown in some studies to identify patients that may benefit from pacing. It appears that more work will need to be done, particularly more work with more sophisticated analytical capabilities that may incorporate strain or other forms of tissue motion analysis before a definitive reliable echocardiogram based index can be achieved. At present, the combination of significant symptoms, significant evidence of an enlarged remodeled heart, an abnormal ECG, and measurements of tissue Doppler time to peak systolic velocity are the best indicators of ventricular dyssynchrony.

Passive Restriction Devices

The concept of inhibiting remodeling by placing a barrier on the outside of the heart has been tested with multiple types of devices. Initial studies, which utilized wrapping of latisimus dorsi muscle around the left ventricle originally hypothesized that the enhanced contractile effect of the skeletal muscle wrap would benefit HF symptoms and reduce remodeling. The contractile benefit appeared minimal. On the other hand, the mere wrapping of this muscle bundle around the heart may have prevented some degree of remodeling. Because of these observations, passive devices, much simpler than biological muscle and its complicated pacing systems, were developed. One of these devices, and perhaps the one most extensively studied to date is the ACORN device, which is a knitted polyester mesh that can be fitted onto the exterior of the heart (Slide 37).[29,30] While it might seem intuitive that a passive restraint device of this nature might cause a restrictive cardiomyopathic picture, studies in animals and also some studies in humans to date have suggested that this is not the case. Indeed, in animal models, passive restraint devices have resulted in inhibition of ventricular enlargement, an attenuation of regional wall stress, and actually an improvement in ejection fraction. Thus, similar to cardiac resynchronization pacing, the passive restraint device appears to cause partial reversal of remodeling, partial enhancement of systolic performance, and most likely over a long term, attenuation of progression of disease. This device has been approved for use in some countries, but a pivotal trial submitted to the United States FDA was turned down and thus the device has not yet reached approval in the United States. Several controversies about the actual endpoint of this pivotal trial appear to have limited the convincing findings necessary for approval.[29,30]

Left Ventricular Assist Device Support

Left ventricular assist devices enhance cardiac output when placed in series with the left ventricle. Typically these devices fill by suctioning blood out of the left ventricular chamber through an apical conduit and then eject into the systemic circulation. These devices, which are now generally electrical and fully implantable allow considerable mobility for the patient. The output of these devices is sufficient to allow a person to function on the device alone. When these devices are placed in patients with very severe systolic performance and low cardiac outputs, typically several morphologic alterations occur soon after the device is placed. The device typically takes over most of the output work of the heart and in very weakly contracting ventricles the aortic valve never opens after the device is turned on. Flow velocities occur entirely because of device performance. As the load is taken off the left ventricle to be a pump and the left ventricle becomes predominantly a conduit, there are substantial reductions in ventricular mass that occur. Left ventricular chamber size usually substantially decreases because the pre-load augmentation effect

is essentially eliminated by the device. Furthermore, there usually is a substantial change in cardiac geometry back to a much smaller if not near normal shape of the left ventricle. Reports evaluating chamber stiffness have actually shown an increase in chamber stiffness. Studies have also shown that there is actually an increase in extracellular matrix, fibrosis, and cross-linking after devices are placed. Studies of isolated myocytes taken from hearts that have been supported by ventricular assist devices for substantial periods of time in many cases show improved contractile performance, suggesting that enhancement in overall myocyte function may occur over time. There may actually be changes in genomic expression induced by the presence of the LVAD. To date only small numbers of patients have improved to a sufficient degree to have the device explanted and the native heart resume normal performance. Most commonly, patients that can show explantation successfully have had more self-limiting diseases such as myocarditis or thyroid-induced heart failure. Much less common have been improvements in patients who have had longstanding chronic failure due to a slowly progressive dilated cardiomyopathy.[30]

Reconstructive Surgery

In selected individuals, predominantly those that have coronary artery disease, certain types of reconstructive surgery may be of value. The first types of patients to undergo reconstructive surgery were those that had large anterior wall myocardial infarctions who developed large apical aneurysms. These operations took place in the pre-interventional cardiology era when patients suffered myocardial infarctions and had no interventions available to them. Large anterior wall infarcts caused in some cases substantial structural changes and aneurysmal formation which resulted in large mechanically misshapen hearts that were very inefficient. Resection of these aneurysms, which appeared to make good sense, initially was not terribly satisfactory for symptomatic improvement. Later, in the 1980s, there was an increase in sophistication of surgical approaches to ventricular remodeling. Work by several individuals resulted in a more sophisticated reshaping of the left ventricle. These procedures, beginning in the mid 1980s, reconstructed the left ventricle, generally by not only resecting a large aneurysm but also by placing some sort of patch over the areas of scar and excluding the large dysfunctional areas of scar. Importantly, however, the shape of the ventricle was modified to make it much closer to a normal shape as opposed to simple aneurysmectomy operations. Also, the operation was typically combined with coronary artery bypass surgery to enhance overall perfusion and also combined in many cases with mitral valve repair to reduce the severity of mitral insufficiency if present. An example of this type of operation is shown in Slide 38. This is an example of the Dor operation. Overall hospital mortality for these types of operations can be substantial. In the series reported by Dor, his overall operative mortality was approximately 7.3%, but it was much higher, at

13%, in patient with very poor ejection fractions (<30), but much lower in patients with somewhat better preserved ventricular function preoperatively. The net result of these operations has been an improvement in ventricular shape and also an improvement in ventricular performance with a typical increase in ejection fraction of 10-15 points. Thus, surgical remodeling when carefully performed appears to be of benefit in highly selected patients.[31,32]

Less selective size reduction of the ventricle, as proposed by Batista, has had widely variable results. This operation enjoyed a brief period of intense investigation following the introduction of the procedure by Batista. In general, the results of this operation have shown that some patients benefit greatly but many other patients show no lasting benefit. Additionally, the mortality rates of this operation appear to be quite high and initial highly successful results presented by Batista have been difficult to replicate in other centers.[32]

Conclusions

This brief overview of cardiac remodeling has attempted to review basic aspects of the remodeling response to ventricular injury and show that the response is a complex and coordinated procedure that occurs at the genomic, molecular, cellular, chamber, and circulatory levels. Successful treatment of patients that have heart failure and ventricular remodeling involves comprehensive evaluation of the severity of the remodeling, careful evaluation of the underlying etiology, and basic medical therapy in all patients, since there are many commonalities to the remodeling response. Use of additional therapies, particularly those involving placement of devices, assist pumps, passive restraint devices, surgical revascularization, or surgical resection of parts of the left ventricle require very careful consideration and evaluation of the underlying etiology and careful assessment of what the potential consequence of this intervention may be. Much progress has been made in understanding and initiating treatment for patients with dilated and dysfunction hearts, but much more needs to be learned and more innovative therapies evaluated to further enhance the therapy of these patients with very severe cardiac disease.

References

1. Packer M. The neurohormonal hypothesis: a theory to explain the mechanism of disease progression in heart failure. J Am Coll Cardiol 1992; 20:248-254.
2. Mann DL, Bristow MR. Mechanisms and models in heart failure: the biomechanical model and beyond. Circulation 2005; 111:2837-2849.
3. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol 2000; 35:569-582.
4. Gerdes AM. Cardiac myocyte remodeling in hypertrophy and progression to failure. J Card Fail 2002; 8:S264-S268.
5. Li F, Wang X, Yi XP, Gerdes AM. Structural basis of ventricular remodeling: role of the myocyte. Curr Heart Fail Rep 2004; 1:5-8.
6. Stowasser M. New perspectives on the role of aldosterone excess in cardiovascular disease. Clin Exp Pharmacol Physiol 2001; 28:783-791.
7. Brown RD, Ambler SK, Mitchell MD, Long CS. The cardiac fibroblast: therapeutic target in myocardial remodeling and failure. Annu Rev Pharmacol Toxicol 2005; 45:657-687.
8. Anversa P, Olivetti G, Capasso JM. Cellular basis of ventricular remodeling after myocardial infarction. Am J Cardiol 1991; 68:7D-16D.
9. Francis GS, McDonald KM. Left ventricular hypertrophy: an initial response to myocardial injury. Am J Cardiol 1992; 69:3G-7G.
10. Bristow MR. beta-adrenergic receptor blockade in chronic heart failure. Circulation 2000; 101:558-569.
11. Carabello BA. Concentric versus eccentric remodeling. J Card Fail 2002; 8:S258-S263.
12. Hunt SA, Abraham WT, Chin MH, Feldman AM, Francis GS, Ganiats TG, Jessup M, Konstam MA, Mancini DM, Michl K, Oates JA, Rahko PS, Silfer MA, Stevenson LW, Yancy CW. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Update the 2001 Guidelines for the Evaluation and Management of Heart Failure). American College of Cardiology Web Site. Available at www.acc.org/clinical/guidelines/failure//index.pdf . 2005.
13. Grayburn PA, Appleton CP, DeMaria AN, Greenberg B, Lowes B, Oh J, Plehn JF, Rahko P, St John SM, Eichhorn EJ. Echocardiographic predictors of morbidity and mortality in patients with advanced heart failure: the Beta-blocker Evaluation of Survival Trial (BEST). J Am Coll Cardiol 2005; 45:1064-1071.

14. Pfeffer MA, Braunwald E. Ventricular remodeling after myocardial infarction. Experimental observations and clinical implications. Circulation 1990; 81:1161-1172.
15. Sato Y, Yamada T, Taniguchi R, Nagai K, Makiyama T, Okada H, Kataoka K, Ito H, Matsumori A, Sasayama S, Takatsu Y. Persistently increased serum concentrations of cardiac troponin t in patients with idiopathic dilated cardiomyopathy are predictive of adverse outcomes. Circulation 2001; 103:369-374.
16. Doust JA, Pietrzak E, Dobson A, Glasziou P. How well does B-type natriuretic peptide predict death and cardiac events in patients with heart failure: systematic review. BMJ 2005; 330:625.
17. Touchstone DA, Beller GA, Nygaard TW, Tedesco C, Kaul S. Effects of successful intravenous reperfusion therapy on regional myocardial function and geometry in humans: a tomographic assessment using two-dimensional echocardiography. J Am Coll Cardiol 1989; 13:1506-1513.
18. Marino P, Zanolla L, Zardini P. Effect of streptokinase on left ventricular modeling and function after myocardial infarction: the GISSI (Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico) Trial. J Am Coll Cardiol 1989; 14:1149-1158.
19. Flather MD, Yusuf S, Kober L, Pfeffer M, Hall A, Murray G, Torp-Pedersen C, Ball S, Pogue J, Moye L, Braunwald E. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. Lancet 2000; 355:1575-1581.
20. Sharpe N. Pharmacologic effects on cardiac remodeling. Curr Heart Fail Rep 2004; 1:9-13.
21. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, Bittman R, Hurley S, Kleiman J, Gatlin M. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 2003; 348:1309-1321.
22. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, Palensky J, Wittes J. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. Randomized Aldactone Evaluation Study Investigators. N Engl J Med 1999; 341:709-717.
23. Wong M, Staszewsky L, Latini R, Barlera S, Volpi A, Chiang YT, Benza RL, Gottlieb SO, Kleemann TD, Rosconi F, Vandervoort PM, Cohn JN. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. J Am Coll Cardiol 2002; 40:970-975.
24. McMurray JJ, Ostergren J, Swedberg K, Granger CB, Held P, Michelson EL, Olofsson B, Yusuf S, Pfeffer MA. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. Lancet 2003; 362:767-771.

25. Lowes BD, Gilbert EM, Abraham WT, Minobe WA, Larrabee P, Ferguson D, Wolfel EE, Lindenfeld J, Tsvetkova T, Robertson AD, Quaife RA, Bristow MR. Myocardial gene expression in dilated cardiomyopathy treated with beta-blocking agents. N Engl J Med 2002; 346:1357-1365.
26. Taylor AL, Ziesche S, Yancy C, Carson P, D'Agostino R, Jr., Ferdinand K, Taylor M, Adams K, Sabolinski M, Worcel M, Cohn JN. Combination of isosorbide dinitrate and hydralazine in blacks with heart failure. N Engl J Med 2004; 351:2049-2057.
27. Bax JJ, Abraham T, Barold SS, Breithardt OA, Fung JW, Garrigue S, Gorcsan J, III, Hayes DL, Kass DA, Knuuti J, Leclercq C, Linde C, Mark DB, Monaghan MJ, Nihoyannopoulos P, Schalij MJ, Stellbrink C, Yu CM. Cardiac resynchronization therapy: Part 1--issues before device implantation. J Am Coll Cardiol 2005; 46:2153-2167.
28. Bax JJ, Abraham T, Barold SS, Breithardt OA, Fung JW, Garrigue S, Gorcsan J, III, Hayes DL, Kass DA, Knuuti J, Leclercq C, Linde C, Mark DB, Monaghan MJ, Nihoyannopoulos P, Schalij MJ, Stellbrink C, Yu CM. Cardiac resynchronization therapy: Part 2--issues during and after device implantation and unresolved questions. J Am Coll Cardiol 2005; 46:2168-2182.
29. Mann DL, Acker MA, Jessup M, Sabbah HN, Starling RC, Kubo SH. Rationale, design, and methods for a pivotal randomized clinical trial for the assessment of a cardiac support device in patients with New York health association class III-IV heart failure. J Card Fail 2004; 10:185-192.
30. Matiwala S, Margulies KB. Mechanical approaches to alter remodeling. Curr Heart Fail Rep 2004; 1:14-18.
31. Dor V. Surgical remodeling of left ventricle. Surg Clin North Am 2004; 84:27-43.
32. Lee R, Hoercher KJ, McCarthy PM. Ventricular reconstruction surgery for congestive heart failure. Cardiology 2004; 101:61-71.