Function of the Cardiac Myocyte in the Conundrum of End-Stage, Dilated Human Heart Failure

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Chronic heart failure is a phenotype that marks the final common pathway in a diversity of specific cardiovascular disease states, eg, severe coronary ischemia and myocardial infarction, and chronic hypertension, or it can be idiopathic in nature. A trilogy of clinical signs that includes reduced systolic myocardial function, increased diastolic filling pressure, and an increased likelihood for the occurrence of cardiac arrhythmias is eventually accompanied by a markedly dilated heart. The specific role of cardiac myocyte dysfunction in progressive cardiac dilatation that heralds the end-stage of chronic heart failure is 1 facet of the conundrum (Hasenfuss et al1) of the end-stage dilated heart. In this issue of Circulation, Hasenfuss et al1 have studied cardiac muscle isolated from the left ventricle of end-stage, dilated cardiomyopathic hearts removed from patients and cardiac muscle from control, non–heart-failure organ donors in an attempt to discover mechanisms that may underlie cardiomyocyte dysfunction in chronic end-stage heart failure.

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As a platform for the discussion of their study, let us first acknowledge that a plethora of hypotheses, in addition to progressive myocyte dysfunction, have been put forth to explain the progressive functional demise and cardiac remodeling and dilatation that characterize end-stage heart failure. These hypotheses were originally cast from observations in heart failure in animal models, including those resulting from chronic experimental mechanical (pressure or volume) overload or chronic ischemia and those resulting from naturally occurring heart failure in specific genetic strains of rodents (eg, the Syrian hamster; the old, spontaneously hypertensive, obese, or diabetic rat; and more recently, heart failure in specific genetic strains of rodents genetically manipulated mice). In most of these models, progressive cardiac dilatation and functional demise eventually occur. Studies that have attempted to understand the conundrum of the evolution to the progressively dilated phenotype have focused on a diverse array of specific changes in structure (size, shape, and number) or function of cardiac myocytes or of the matrix in which these and the microvasculature reside. Herein, we discuss a number of plausible reasons for progressive cardiac decompensation, including the functional alterations described in the article by Hasenfuss et al.1 We also identify important questions that need to be answered if the conundrum of the failing heart is to be resolved.

Cardiac structural changes that accompany heart failure, eg, changes in cardiac myocyte number and size, matrix production, and angiogenesis, are generally thought to be under the combined control of neurotransmitters (eg, norepinephrine), growth factors, (eg, angiotensin II, endothelin, insulin-like growth factor, and fibroblast growth factor), cytokines, (eg, tumor necrosis factor-α), and mechanical strain. During cardiac remodeling in the context of hypertrophy and failure, these factors, as well as interactions among them, cast a risky scenario in that while some myocardial cells increase in size and some vascular cells proliferate, others succumb to apoptosis or necrosis; there is also some evidence that myocardial cells, heretofore considered to be terminally differentiated, may successfully reenter the cell cycle in response to these stimuli. The net result of the remodeling process that characterizes end-stage cardiac dilatation, however, appears to be a reduction in cardiac myocyte number, side-to-side slippage of myocytes, a reduction in contractile filament mass, and proliferation of interstitial matrix, which includes focal and perivascular fibrosis. Progressively abnormal cardiac pump function leading to the end-stage dilated heart may be explicable, in part, on the basis of a feed-forward structural remodeling in a ventricle coupled with a progressive mismatch of cardiac and vascular mechanical loading. Thus, a gradual, progressive reduction in myocyte number and an increase in matrix result in a gradual, progressive reduction in cardiac pump function. This causes progressive renal fluid retention, which maintains an increased cardiac blood volume, resulting in a sustained increase in both diastolic and systolic stretch on the myocardium. A vicious circle of growth factor/cytokine release, leading to additional cell dropout, may then occur, placing additional stretch on surviving myocytes and fibroblasts, leading to additional cytokine/growth factor–induced cell death, among other things.

That reduced myocyte function might be thought of as among the initial stimuli, if not the initiating stimulus, for the cardiac structural remodeling noted above follows intuitively from a multitude of observations in which the heart has been made to fail acutely by interruption of normal myocardial energetic mechanisms or by tinkering with regulation of myocyte Ca²⁺ levels (Ca²⁺ levels that are either too high or too low can do it!). The traditional view of cardiac myocyte responses to chronic stimuli associated with pathophysiol-
ical mechanisms of cardiovascular diseases, eg, enhanced mechanical load or growth factor activation, is a compensatory change in myocyte cell size and a shift to an “adaptive functional phenotype.” A common, adaptive cardiac myocyte phenotype accompanying an enlargement in cell size in response to diverse stimuli that result in increased ventricular wall stress, eg, hypertension or local remodeling after a myocardial infarction, is one that permits sustained force-bearing capacity and spares energy and includes changes in the expression of proteins involved in the regulation of cell ion or energy regulation (see below). This adaptive phenotype is generally characterized by a prolonged action potential (AP) and a more slowly developing but more sustained Ca^{2+} transient and contraction after excitation. A substantial and somewhat specific reduction in the myocyte response to demand for increased performance in response to sympathetic stimulation also accompanies this adapted state, even though the heart need not be dilated at this point. This pattern of functional adaptations can often be linked to changes in the levels of mRNA coding for specific proteins and protein levels, eg, reduction in cardiac α-myosin and SERCA 2 and an increase in Na-Ca exchanger, among others.

A very similar “adaptive” cardiac phenotype usually accompanies aging in healthy humans and animals, even in the absence of heart disease. Given the demographic imperatives that ≈90% of individuals in our society who have a diagnosis of chronic heart failure are >70 years of age and that heart failure is diagnosed in ≈8 of every 100 individuals above the age of 70 years, the interactions of specific pathophysiological mechanisms that underlie cardiac failure and those that cause cardiovascular changes that occur in healthy individuals during the aging process need to be addressed to eventually solve the puzzle of progressive heart failure.

The evolution of myocyte function from the adapted phenotype to that of end-stage, dilated chronic heart failure might be construed to occur on the basis of progressive saturation and failure of biophysical mechanisms that regulate myocyte adaptive function, which initially prevails in the compensated state. In addition to loss of or saturation of myocyte adaptations, reductions in myocardial adaptive capacity could follow from progressive myocyte cell dropout (necrosis or apoptosis) and matrix accumulation, among other factors, as discussed above. The task at hand is to discover whether the cardiac myocyte is the perpetrator or the victim; ie, does progressive myocyte loss precede and cause progressive cardiac dilatation, or does progressively abnormal myocyte function lead to end-stage cardiac dilatation, which then triggers cell loss? A plausible but heretofore unarticulated hypothesis of how this occurs might be as follows: dysfuncction of some myocytes, sufficient to reduce their contractility to a point at which these cells are stretched by stronger neighboring cells, triggers their elimination (by apoptosis or necrosis). Cell death in this scenario might in fact be construed as an adaptive maneuver, because the continued presence of weakly contracting cells reduces ensemble myocyte function and thus reduces myocardial performance.

The article by Hasenfuss et al focuses on mechanisms that may lead to weakened cardiac myocyte function in the end-stage, dilated human heart. Cardiac myocyte function is regulated by intrinsic mechanisms that govern Ca^{2+} signaling, and many of these mechanisms are modulated by adrenergic and other receptor stimulation. Whether there is too much or too little myocyte Ca^{2+} signaling in chronic end-stage failure has been a perennially debated aspect of the puzzle of end-stage heart failure. An explanation often raised for a progressive decline in myocardial performance and cardiac dilatation is a progressive reduction (desensitization) in β-adrenergic responsiveness. This explanation implicitly assumes that Ca^{2+} loading and contractility of individual myocytes has not reached its maximum and that these cells could be “rescued” if the β-adrenergic system were “made new.” A contrasting opinion is that the progressive reduction in adrenergic responsiveness is “protective” to a myocardium in which myocytes are already “maxed out,” energetically or otherwise, and that additional Ca^{2+} loading, ie, Ca overload, leads to cellular demise. The beneficial role of β-adrenergic receptor antagonists in patients with chronic heart failure appears to underscore the role of overstimulation of this pathway in progressive cardiac deterioration in humans. In contrast, maneuvers that enhance β-adrenergic signaling in transgenic mice cure dilated cardiomyopathy created by the “heavy hand” of first-generation mouse genetics. Thus, we are still unenlightened with respect to which viewpoint of adrenergic stimulation is correct. Regardless, progressive cardiac dilatation leading to terminal decompensation is accompanied by marked increases in plasma catecholamines and presumably marked increases in their concentration in the pericellular space. Chronic overstimulation of catecholamine receptors not only desensitizes receptor signaling but also may contribute to myocyte death due to necrosis or apoptosis. Other cytokines/growth factors that become elevated in end-stage failure have also been implicated in myocyte death.

Many studies, including that by Hasenfuss et al, have attempted to define non–receptor-mediated, ie, intrinsic, mechanisms that underlie altered Ca^{2+} regulation in the failing cardiac myocyte. These studies have used biophysical, biochemical, molecular, and genetic approaches in normal and failing human tissue and in animal models of human diseases. Several major candidate molecules and their associated physiological processes involved in myocyte Ca^{2+} regulation in heart failure have been studied, and most have been found to be quantitatively or qualitatively modified. This is not surprising given the fact that the heart adapts, as noted above, and likely eventually maladapts via a pattern of altered gene and protein expression, resulting in an altered pattern of structure and function (phenotype). Because there are many redundancies in regulatory mechanisms for Ca^{2+}, and because most processes that are involved in the control of cellular Ca^{2+} work in concert with one another, a modification in the overall function of 1 molecule is likely compensated for by changes in the amount or function of others. This is the main premise of classic cardiac adaptation. Thus, it is extremely unlikely that a change in 1 molecule or process (the Holy Grail hypothesis) can explain the “electromechanical phenotype” of the failing heart. Recent approaches to the manipulation of mouse genetics, expecting that a single abnormality will explain the ensuing cardiac phenotype, seem to have overlooked this reality.
Previous studies have delineated some components of the altered pattern of myocyte \( \text{Ca}^{2+} \) regulation in human heart failure that contribute to cardiac pump dysfunction. The pioneering work of the Morgan laboratory showed that changes in myocyte \( \text{Ca}^{2+} \) regulation were primarily responsible for the slow relaxation of failing human myocardium. Subsequent studies in human tissues and cells and in animal models confirmed and expanded on these observations. These studies have shown that reduced systolic force generation in the failing heart primarily results from a decreased peak systolic \( \text{Ca}^{2+} \) level, and slowed relaxation is best explained by slow decay of the \( \text{Ca}^{2+} \) transient. A number of studies suggest that lower than normal peak systolic \( \text{Ca}^{2+} \) of the failing myocytes results from a reduced amount of \( \text{Ca}^{2+} \) released from the sarcoplasmic reticulum (SR), and the slower than normal rate of decay of the \( \text{Ca}^{2+} \) transient is produced by a diminished rate of SR \( \text{Ca}^{2+} \) uptake. In failing rat hearts, a mechanism for reduced SR \( \text{Ca}^{2+} \) release appears to be abnormal coupling of trigger \( \text{Ca}^{2+} \) (L-type \( \text{Ca}^{2+} \) current) to SR \( \text{Ca}^{2+} \) release. However, in failing human myocytes decreased SR \( \text{Ca}^{2+} \) loading appears to be the primary explanation for decreased SR \( \text{Ca}^{2+} \) release. A reduction of the SR \( \text{Ca}^{2+} \) load in failing human heart appears to be the consequence of reduced SR \( \text{Ca}^{2+} \) ATPase protein; however, this is not a universal finding (see Reference 16). The consensus of studies in failing human tissues and cells performed to date is that alterations in SR function play a major role in the changes in the \( \text{Ca}^{2+} \) transient of the failing human myocyte. An often-ignored corollary of this conclusion is that the \( \text{Ca}^{2+} \) transient of failing myocytes will be more likely to be influenced by transsarcolemmal \( \text{Ca}^{2+} \) influx and efflux.

As the plot of the altered \( \text{Ca}^{2+} \) regulation in myocytes of the chronically failing human myocyte thickened, it was realized that to define alterations in the kinetics of \( \text{Ca}^{2+} \) regulation, it is necessary to increase the pacing rate of isolated human cardiac preparations (afforded by use of thinner muscle preparations or single cardiac cells studied at 37°C). It was then nearly universally found that human end-stage myocardium has a negative rather than a normal force-frequency relationship and that this is accompanied by a frequency-dependent reduction in the systolic \( \text{Ca}^{2+} \) transient and an elevation in diastolic \( \text{Ca}^{2+} \) and force. The specific focus of the article by Hasenfuss et al is on regulation of cardiac cell \( \text{Ca}^{2+} \) during pacing at different stimulation frequencies. These investigators discovered that different subsets of human muscles they studied exhibited variable elevations of cytosolic \( \text{Ca}^{2+} \) in the diastolic period and that systolic \( \text{Ca}^{2+} \) levels and force varied inversely with elevation in diastolic \( \text{Ca}^{2+} \). The authors implicate differential levels of Na–Ca–exchange protein in this behavior.

The Na–Ca exchanger, because of its unique functional characteristics, is the “switchboard” for cardiocyte \( \text{Na}^{+} \), \( \text{Ca}^{2+} \), and pH regulation and plays an important role in controlling the strength of myocardial contraction during stimulation at different frequencies. The sarcolemmal Na–Ca exchanger is a large membrane protein that actively transports \( \text{Na}^{+} \) or \( \text{Ca}^{2+} \) but does not directly utilize ATP in the process. Instead, it uses the energy in either the \( \text{Na}^{+} \) or the \( \text{Ca}^{2+} \) electrochemical gradient to move either \( \text{Na}^{+} \) ions or \( \text{Ca}^{2+} \) ion against their electrochemical gradients. An important feature of the Na–Ca exchanger is that it can move \( \text{Ca}^{2+} \) (and \( \text{Na}^{+} \)) either into or out of the cell. The direction of net \( \text{Ca}^{2+} \) transport is determined by the transmembrane \( \text{Na}^{+} \) and \( \text{Ca}^{2+} \) concentration gradients and the membrane potential. Therefore, the activity of the Na–Ca exchanger is modulated by and modulates the activity of other \( \text{Na}^{+} \) and \( \text{Ca}^{2+} \) transporters such as the Na–K ATPase, the Na–H exchanger, and the SR \( \text{Ca}^{2+} \) pump. During the AP upstroke and initial repolarization, the electrochemical gradients of \( \text{Na}^{+} \) and \( \text{Ca}^{2+} \) favor reverse-mode Na–Ca flux, ie, the exchanger causes calcium influx. Recent studies suggest that \( \text{Ca}^{2+} \) influx via L-type \( \text{Ca}^{2+} \) channels increases in end-stage human heart failure and that this increase is produced by AP prolongation, a common and prominent feature of the failing myocyte. A debate continues to rage regarding the interplay of \( \text{Ca}^{2+} \) influx via the exchanger and influx via L-type \( \text{Ca}^{2+} \) channels in effecting \( \text{Ca}^{2+} \) release/\( \text{Ca}^{2+} \) loading of the SR. Regardless of the pathway by which \( \text{Ca}^{2+} \) enters the cytosol from outside the cell during the AP, to maintain \( \text{Ca}^{2+} \) homeostasis in a steady state, it must be removed via the Na–Ca exchanger as soon as the electrochemical gradient permits forward-mode exchange, usually during AP repolarization and throughout diastole. In cardiac muscle, the Na–Ca exchanger is the principle mechanism for \( \text{Ca}^{2+} \) efflux (so-called forward-mode exchange), because in this tissue, sarcolemmal \( \text{Ca}^{2+} \) ATPase is not found in high abundance.

An example of the switchboard function of the Na–Ca exchanger in the human heart is the positive inotropic effect that results after the stimulation rate is increased (Bowditch treppe). An increase in \( \text{Na}^{+} \) influx due to an increased heart rate results in an increase in cytosolic \( \text{Na}^{+} \) that is only partially compensated for by an increase in Na–K ATPase activity (partial Na–K ATPase inhibition by cardiac glycosides produces a similar effect as an increase in the pacing rate to elevate intracellular \( \text{Na}^{+} \)). A persistent reduction in the \( \text{Na}^{+} \) electrochemical gradient leads to a net cell \( \text{Ca}^{2+} \) retention via the Na–Ca exchanger (greater \( \text{Ca}^{2+} \) influx and less \( \text{Ca}^{2+} \) efflux), which produces an increase in \( \text{Ca}^{2+} \) within the cytosol and within the SR. Thus, the Na–Ca exchanger is a major regulator of cytosolic and stored \( \text{Ca}^{2+} \) in cardiac myocytes and therefore is a major determinant of both systolic and diastolic function. In their study, Hasenfuss et al attribute the phenotypic discrimination of differential patterns of \( \text{Ca}^{2+} \) ion regulation in different subsets of muscle removed from failing hearts that they observed to differential patterns of Na–Ca–exchanger protein regulation. Other studies of failing human myocardium have routinely shown that Na–Ca–exchanger mRNA and protein are increased, but the study by Hasenfuss et al specifically shows that variations in the concentration of Na–Ca–exchanger protein among muscles from failing human hearts are inversely related to variations in the frequency-dependent increase in diastolic \( \text{Ca}^{2+} \), which results in diastolic dysfunction. These results strongly support the idea that the Na–Ca exchanger has a central involvement in the heart failure cardiocyte phenotype and further support the idea that the Na–Ca exchanger plays a more significant role in the decay of the \( \text{Ca}^{2+} \) transient in the chronic end-stage failing heart than in normal myocardium. The fact that...
increases in diastolic Ca\(^{2+}\) levels in the study by Hasenfuss et al\(^1\) were related to reductions in systolic Ca\(^{2+}\) exemplifies an Na-Ca–exchanger switchboard function, ie, to link diastolic and systolic function. The interplay between Na-Ca and SR Ca\(^{2+}\) pump determines how much Ca\(^{2+}\) can be loaded back into the SR during a given heartbeat and how much remains in the cytosol between beats. It is not clear from the results of Hasenfuss et al whether the SR Ca\(^{2+}\) load becomes depleted to a greater extent in muscles from hearts in which the exchanger is more abundant. This is plausible given the frequency-dependent decrease in \(I_{na}\) in failing human heart cells.\(^2\)

Studies in animal models indicate that an increase in Na-Ca–exchanger expression is part of the adaptive pattern that occurs in response to increased demands for myocyte performance, long before heart failure ensues.\(^2\) Studies in transgenic mice with genetically induced overexpression of the Na-Ca exchanger show that increased exchanger expression per se does not cause the contractile disturbances of the failing human myocytes, because contractility in these mice is equal to or greater than normal and is not associated with cardiac hypertrophy or heart failure.\(^3\) Changes in cellular Ca\(^{2+}\) regulation in the mouse are not easily interpretable with respect to the phenotypic pattern of end-stage heart failure in humans. Extrapolation of data in mice to the human case is particularly tempered by the fact that the Na-Ca exchanger likely functions in a significantly different fashion in small mammals, which have fast heart rates and very short AP durations compared with humans. Specifically, in mice, the AP repolarizes within a few milliseconds, ie, long before the Ca\(^{2+}\) transient begins to decay. Thus, the Na-Ca exchanger likely functions in the forward (Ca\(^{2+}\) efflux) mode throughout the Ca\(^{2+}\) transient. This means that in mice, forward-mode (Ca\(^{2+}\) efflux) exchange, SR Ca\(^{2+}\) uptake mechanisms, and contractile proteins compete for Ca\(^{2+}\) that enters the cytosol. In this species, the Ca\(^{2+}\) transport rate of the SR must be substantially greater than that of the Na-Ca exchanger to prevent the exchanger from depleting SR Ca\(^{2+}\) stores. In contrast, in humans, the AP duration is greater than the duration of the Ca\(^{2+}\) transient, and thus, the depolarized membrane potential favors forward-mode rather than reverse-mode Na-Ca–exchanger activity. Therefore, during the human Ca\(^{2+}\) transient forward mode, exchange does not compete with SR Ca\(^{2+}\) uptake until the terminal portions of the transient that coincide with final repolarization of the AP. Given the fundamental differences in cardiocyte Ca\(^{2+}\) regulation in mice and humans, it is likely each will have unique adaptations to cardiovascular stress. Additionally, because the molecules that regulate Ca\(^{2+}\) homeostasis in cardiac cells function as a team, as noted above, each mouse with a cardiac phenotype resulting from experimental manipulation of a single gene requires rigorous biophysical phenotyping to discover not only the physiological effect of upregulation or downregulation of the manipulated gene, but also the presence and effects of adaptations that occur in response to genetic manipulation.\(^2\) in other “team-member molecules” that regulate cell function. Unfortunately, many of these adaptations to gene manipulation are unpredictable, are rarely considered, or are ignored because they are tedious to discover.

Studies of calcium regulation in both animal and human end-stage cardiac myocytes have generally assumed that myocytes are uniform with respect to calcium regulation. However, structural and functional heterogeneity within and among cells likely characterizes the end-stage failing heart and thus extends the domain of its conundrum. It has been shown experimentally that small increases in cell Ca\(^{2+}\) that exceed those required for maximum contractility result in marked heterogeneity in local levels of Ca\(^{2+}\) within the cytoplasm and within intracellular cardiac organelles.\(^2\) In the accompanying article, Hasenfuss et al\(^1\) generally interpret the large, frequency-dependent increases in diastolic force to be due to a Ca\(^{2+}\)-dependent myofilament interaction caused by a steady increase in diastolic cytosolic [Ca\(^{2+}\)], that is, to uniform elevations in Ca\(^{2+}\) throughout the cells of the muscle preparation used in their study. However, when diastolic Ca\(^{2+}\) becomes elevated, the SR continues to pump Ca\(^{2+}\) and can spontaneously (rather than under the command of an AP) release Ca\(^{2+}\) back into the cytosol. This uptake and spontaneous Ca\(^{2+}\) release occurs asynchronously among regions within given cells and asynchronously among cells producing local gradients of Ca\(^{2+}\). The frequency of occurrence of such localized spontaneous oscillatory Ca\(^{2+}\) release, which determines the extent of synchronization among local regions, increases with cell Ca gain until energy becomes depleted.\(^5\) When an AP occurs under these conditions, some regions will have a reduced local \(I_{na}\)-induced SR Ca\(^{2+}\) release (owing to localized residual inactivation of L-type Ca channels and to local SR Ca\(^{2+}\) depletion, both due to spontaneous SR Ca\(^{2+}\) release). Both of these effects that accompany localized gradients in diastolic Ca\(^{2+}\) lead to reduction in the summated systolic SR Ca\(^{2+}\) release (global Ca\(^{2+}\) transient) and to a weaker contraction.\(^2\) In fact, oscillatory Ca\(^{2+}\) release due to this mechanism can produce the trilogy of heart failure manifestations noted above, ie, Ca\(^{2+}\)-dependent arrhythmias, reduced systolic function, and increased diastolic tone due to increased diastolic cytosolic Ca\(^{2+}\) levels.\(^3\)

In summary, there is a great deal more to be understood regarding mechanisms of abnormal Ca\(^{2+}\) regulation in myocytes from the failing human heart and the specific role of the Na-Ca exchanger in this. Studies that correlate Na-Ca protein abundance with muscle function, eg, that by Hasenfuss et al,\(^1\) are a welcomed first step in the process. Additional rigorous biophysical and energetic phenotyping is needed because in addition to protein abundance, the activity of the exchanger depends on membrane potential and Na\(^+\), Ca\(^{2+}\), and H\(^+\) gradients. One aspect of Na-Ca–exchanger function in human myocytes that has been particularly ignored to date is that it can also operate in a reverse mode to load the myocyte with Ca\(^{2+}\). Reverse-mode exchange is promoted by depolarization, elevation in cell Na\(^+\), and low cytosolic free Ca\(^{2+}\). Failing human myocytes have longer AP durations and smaller Ca\(^{2+}\) transients than normal myocytes. Therefore, Ca\(^{2+}\) influx via reverse-mode Na-Ca exchange should be increased in failing myocytes and, in the face of reduced SR function and Ca\(^{2+}\) loading and release, could contribute to slow relaxation, diastolic cytosolic Ca\(^{2+}\) overload, and spontaneous diastolic
SR Ca\(^{2+}\) release. The presence and significance of heterogeneous Ca\(^{2+}\) regulation within and among failing myocytes with respect to systolic and diastolic dysfunction need to be defined. Methods for detection of local spontaneous Ca\(^{2+}\) release have been devised for preparations varying from single cells to intact hearts and should be used in future studies that seek to solve the conundrum of myocyte pathophysiology in the end-stage failing myocardium.

A well-defined body of scientific research points to the fact that the heart adapts or maladapts in the context of altered patterns of gene/protein/ion regulation rather than by unique alteration in singe genes or proteins. Clearly, studies in experimental animal heart failure models collectively portray many features observed to date in the chronic human end-stage heart and will continue to be invaluable in this regard. But will cardiac phenotypes of altered myocyte structure and function that result from genetic manipulation of single genes in mice be as instructive as other animal models of heart failure in this regard? Surely this requires further proof, given our substantial investment in mouse genetics. Recent advances in “fingerprinting” the differences in gene expression in heart failure and simultaneous characterization of resultant phenotypes will be invaluable to both the genetic and more traditional models of chronic heart failure research.

There are a number of additional issues that must be addressed in the quest to solve the conundrum of the end-stage dilated heart and the progression of heart failure to the end stage. Does progressive cardiac dilatation occur because of a progressive deterioration of myocyte function or because of a reduction in myocyte number? If a progressive myocyte loss does occur, is it an adaptation to preserve function of less-affected cells, or is it maladaptation resulting in further dilatation? How does excessive matrix production or impaired angiogenesis contribute to progressive cardiac dilatation?

References


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