The incidence of death from cardiac hypertrophy and heart failure has increased steadily over the past 25 years despite the overall decline in mortality from heart disease during the same period. As of 1990, heart failure was responsible for more than 400,000 deaths per year and was the most common discharge diagnosis in the Medicare population.1 Overall, patients with heart failure have a 5-year mortality rate of 50%. Patients with New York Heart Association class III and IV heart failure have a 2-year mortality approaching 50% despite nearly optimal treatment with ACE inhibitors, diuretics, and digoxin.2 Therefore, it is fair to say that the prevalence of heart failure has reached epidemic proportions in this country and in most industrialized western societies. Clearly, a better understanding of the primary mechanisms that underlie the contractile abnormalities of the failing heart is needed to develop new therapeutic strategies for the treatment of existing heart failure and more effective guidelines for the prevention of heart failure.

After nearly 3 decades of intensive investigation, the precise mechanisms that underlie the contractile abnormalities of cardiac hypertrophy and heart failure remain elusive. The distinction between true mechanisms and mere markers of disease has been particularly difficult in heart failure, because the complex cascade of physiological, neurohumoral, and biochemical abnormalities undoubtedly represents the complex interaction of a multitude of environmental and genetic factors. Obviously, making this distinction has far-reaching therapeutic implications. Fresh insights regarding the cellular and molecular bases of heart failure have come from very recent work in the molecular genetics of human cardiomyopathy and from transgenic mouse models with mutations of muscle-specific genes. For example, several recent studies have exploited transgenic technologies to identify the precise cellular abnormality(ies) responsible for the observed alterations in [Ca2+]i. However, recent work has implicated the key role of the sarcoplasmic reticulum (SR) in mediating many of the changes in [Ca2+]i transient observed in heart failure.3 In normal cardiac muscle, calcium entry through sarcolemmal L-type calcium channels triggers the release of a much larger amount of calcium stored in the SR, thereby activating contraction. Relaxation is mediated predominantly by the uptake of calcium into the SR by the SR calcium ATPase pump (SERCA2). Phospholamban and its state of phosphorylation regulate the activity of SERCA2. Stimulation of the β-adrenergic receptor cascade leads to phosphorylation of phospholamban and subsequent relief of its inhibition of SERCA2. Therefore, the phospholamban/SERCA2 interaction controls the calcium content of the SR and ultimately cardiac contractility. In principal, manipulation of SR function through phospholamban phosphorylation and SERCA might restore cardiac contractility and “rescue” the failing heart independently of the inciting mechanism. However, systemic administration of adrenergic agonists provides only transient improvement of contractile dysfunction and has deleterious effects on the prognosis of heart failure. This experience raises the question of whether depressed contractility is truly a mechanism of heart failure or merely a marker of the manifestation of disease. Several recent studies have exploited transgenic technologies to address this question at different levels of the β-adrenergic signaling cascade. The first encouraging result came from the genetic complementary study between β-adrenergic receptor kinase (βARK) inhibitor and muscle lim protein knockout (MLP−/−) mice.12 Overexpression of a βARK inhibitor increased both basal and isoproterenol-mediated contractility and prevented the development of the dilated cardiomyopathy phenotype in the MLP−/− heart.12 At the same level, overexpression of β- adrenergic receptors at low levels restored depressed contractility and prevented the development of mutations in cytoskeletal genes.4,5 In addition, overexpression of different signaling molecules in mouse models leads to cardiac hypertrophy and heart failure.4,6,7 Therefore, it now seems clear that there are multiple parallel pathways to the common phenotype of heart failure.

Profound alterations in systolic and/or diastolic function are the sine qua non of heart failure. Diminished contractile function has been associated with several abnormalities in [Ca2+]i, handling in animal models of heart failure and in failing human hearts.8–11 In the failing heart, resting [Ca2+]i is elevated, the amplitude of the [Ca2+]i transient is decreased, and its duration is prolonged. Previous studies have not identified the precise cellular abnormality(ies) responsible for the observed alterations in [Ca2+]i. However, recent work has implicated the key role of the sarcoplasmic reticulum (SR) in mediating many of the changes in [Ca2+]i transient observed in heart failure.5 In normal cardiac muscle, calcium entry through sarcolemmal L-type calcium channels triggers the release of a much larger amount of calcium stored in the SR, thereby activating contraction. Relaxation is mediated predominantly by the uptake of calcium into the SR by the SR calcium ATPase pump (SERCA2). Phospholamban and its state of phosphorylation regulate the activity of SERCA2. Stimulation of the β-adrenergic receptor cascade leads to phosphorylation of phospholamban and subsequent relief of its inhibition of SERCA2. Therefore, the phospholamban/SERCA2 interaction controls the calcium content of the SR and ultimately cardiac contractility. In principal, manipulation of SR function through phospholamban phosphorylation and SERCA might restore cardiac contractility and “rescue” the failing heart independently of the inciting mechanism. However, systemic administration of adrenergic agonists provides only transient improvement of contractile dysfunction and has deleterious effects on the prognosis of heart failure. This experience raises the question of whether depressed contractility is truly a mechanism of heart failure or merely a marker of the manifestation of disease. Several recent studies have exploited transgenic technologies to address this question at different levels of the β-adrenergic signaling cascade. The first encouraging result came from the genetic complementary study between β-adrenergic receptor kinase (βARK) inhibitor and muscle lim protein knockout (MLP−/−) mice.12 Overexpression of a βARK inhibitor increased both basal and isoproterenol-mediated contractility and prevented the development of the dilated cardiomyopathy phenotype in the MLP−/− heart.12 At the same level, overexpression of β- adrenergic receptors at low levels restored depressed contractility and prevented the development of...
hypertrophy in a heart failure model established by overexpressing G_{aq}.\(^7\) One step below the receptor level, targeted expression of adenyl cyclase increased intracellular cAMP and prevented heart failure in the same G_{aq} cardiac hypertrophy model.\(^4\) Further downstream in the β-adrenergic pathway, both overexpression of SERCA2 and knocking out of phospholamban improved basal contractility in transgenic hearts.\(^15,16\) Indeed, ablation of phospholamban prevented the development of heart failure and restored cardiac function in the MLP\(^{-/-}\) mouse.\(^17\) These transgenic studies support a central role of SR calcium handling as a downstream target of the β-adrenergic signaling pathway in the development of heart failure. These studies also raise the possibility that manipulation of SERCA2/phospholamban activity may both prevent and also truly “rescue” a heart failure phenotype and restore its cardiac function.

In this issue of Circulation, Schmidt et al\(^18\) tested the feasibility of restoring contractile function by overexpressing SERCA2 by a recombinant adenoviral gene transfer approach. They studied senescent rat hearts, which have many of the contractile abnormalities that are characteristic of heart failure, including diminished contraction velocity, prolonged relaxation, attenuated β-adrenergic responsiveness, and diminished content and activity of SERCA2 with no concomitant changes in other calcium regulatory proteins, such as phospholamban, sodium/calcium exchanger, or the ryanodine receptors. Transfection of senescent rat hearts with Ad.SERCA2a effectively restored cardiac function to the level of young adults. Specifically, Ad.SERCA2a transfection restored contraction velocity, shortened relaxation, and raised SERCA2a protein levels to those of young adults. This work has several obvious and important implications. Schmidt et al\(^18\) are the first to truly “rescue” cardiac function in an established disease phenotype.\(^2\) They demonstrate convincingly the therapeutic feasibility of delivering adenoviruses to the heart.\(^3\) Their adenoviral gene transfer approach provides an important confirmation of the previous work in transgenic animals without the potential problem of additional compensatory changes that accompany any genetic manipulation.\(^4\) Their finding that the content of SERCA2a but not phospholamban is diminished in untreated senescent rats supports the hypothesis from transgenic studies\(^17\) that the relative ratio of phospholamban/SERCA2 is an important determinant of cardiac contractility in the normal heart and that alterations in this ratio may be the underlying mechanism of altered contractility in a variety of cardiac pathologies.\(^19\)

Together, the study of Schmidt et al\(^18\) and the body of transgenic studies represent real progress in separating the mechanisms and markers of altered contractility in heart failure. This work supports the common theme that correction of the underlying abnormalities in calcium homeostasis may restore depressed cardiac function resulting from a myriad of distinct causes. Even if the therapeutic application of gene therapy is a long way off, this work supports the strategy of pharmacologically targeting various steps in the pathway(s) that regulate phospholamban/SERCA2 for treatment of heart failure and “rescues” hope that effective new pharmacological therapies may finally be close at hand.

References


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