Maurice et al. recently reported that a global ventricular 10-fold overexpression of the β-2 adrenergic receptor, mediated by the intracoronary injection of an adenoviral vector, can be produced in the rabbit. This overexpression resulted in an increased maximum rate of change in left ventricular pressure, dp/dtmax, both at baseline and in response to isoproterenol infusion at 6 days after transgene delivery, with the enhanced isoproterenol response persisting for up to 21 days. They concluded that genetic modulation to improve the function of the intact heart is feasible. In this issue of Circulation, del Monte et al. describe experiments that indicate that gene therapy can improve failing human cardiac myocyte function. These investigators demonstrated that the abnormal contraction, relaxation, and contraction amplitude-frequency relationship of isolated myocytes obtained from patients with dilated cardiomyopathy could be normalized by transfection of the myocytes in vitro with an adenovirus expressing the sarcoplasmic reticulum (SR) Ca2+-ATPase, SERCA2a; transfection increased Ca2+ ATPase activity by 80%. The enhanced function of the myocytes was associated with corresponding improvements in the kinetics of the Ca2+ transient. The isolated myocyte results confirm previous in vitro findings by Meyer et al. in normal rabbit myocytes that indicated that adenoviral transfection of SERCA2a can improve contraction and relaxation.

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Early studies by Lindenmayer et al.4 suggested that the Ca2+ uptake of isolated SR vesicles was impaired in failing human myocardium, and Grossman et al.5 found that the peak dp/dt of left ventricular pressure decline and the velocity of circumferential fiber lengthening were reduced in patients with congestive cardiomyopathy. Evidence that this impaired relaxation in the failing heart is due to abnormal Ca2+ homeostasis was provided by Gwathmey et al.6 These investigators found that intracellular Ca2+ concentration ([Ca2+]i) transients recorded with the Ca2+ probe aequorin during isometric contraction of myocardium in patients with end-stage failure were markedly prolonged, with a peak and then a secondary “hump” in the [Ca2+]i transient trace, which was associated with a marked prolongation of the time course of the Ca2+ decline and of tension decline. Because the SR Ca2+ ATPase is responsible for 60% to 90% of the [Ca2+]i decline in mammalian ventricular myocytes,7 these results were consistent with impaired function of the SR Ca2+ transport system.

Subsequently, a number of molecular studies in animal models and in human heart failure have suggested that during the process of hypertrophy and progression to failure, a fetal pattern of cardiac myocyte gene expression is activated; this pattern decreases the expression of the SR Ca2+ ATPase and increases the expression of the Na+/Ca2+ exchanger.8,9 Functional studies have also suggested that the decreased activity of SR Ca2+ ATPase is an important contributor to the abnormal contraction of failing human myocardium. For example, Lindner et al.10 showed a reduced SR Ca2+ content in myocytes from patients with terminal heart failure, and Hasenfuss et al.11 reported that the extent of the abnormality of the force-frequency relationship in the failing human myocardium could be correlated with the degree of reduction in the levels of the SR Ca2+ ATPase protein.

However, some studies in the failing human myocardium reported normal protein levels of SR Ca2+ ATPase and normal rates of Ca2+ uptake by vesicle preparations.12 In addition, recent work by Dipla et al.13 in failing human ventricular myocytes demonstrated that increased function of the Na+/Ca2+ exchanger in failing cardiac myocytes, induced perhaps by an increased expression of the exchanger mentioned above and by the prolonged action potential duration that is seen in hypertrophied and failing myocardium, might produce excessive Ca2+ influx on the exchanger during the prolonged action potential plateau. This prolonged influx of Ca2+ could account for the secondary Ca2+ transient hump, which was noted in the initial aequorin experiments of Gwathmey et al.,6 and could also contribute to the prolonged [Ca2+]i transient and impaired relaxation.14 Thus, some uncertainty exists regarding the central role of depressed SR Ca2+ ATPase activity in producing impaired contraction and relaxation in heart failure.

It is important to note that other factors in hypertrophy and failure may influence the Ca2+ sequestering function of the SR pump, independent of the level of SERCA2a expression. These include the leakage of the SR for Ca2+,15 the interaction of phospholamban with SR Ca2+ ATPase1 and, of course, the free energy available to drive the ATP-dependent SR Ca2+ pump. Although the cellular changes associated with heart failure are complex and multifactorial,15 this study by del Monte et al.12 provides strong additional support for the hypothesis that the impaired function of SR Ca2+ ATPase plays an important role in the functional abnormalities observed.

Assuming that impaired Ca2+ sequestration by the SR is involved in the progression to end-stage heart failure, what is the evidence that gene therapy to increase the function of SR Ca2+ ATPase may be effective in the treatment of heart failure?
Some very interesting experiments exist in transgenic mice that are relevant to this question. Crossing the Muscle LIM Protein Knockout (MLPKO) mouse, which develops a dilated cardiomyopathy, with a Bark-1 ct transgenic mouse, in which desensitization of the β receptor (and presumably decreased phospholamban phosphorylation) is prevented, showed that the development of the heart failure phenotype can be prevented.16 Also, enhancing SR Ca²⁺ ATPase function by crossing the MLPKO with a phospholamban knockout animal can also prevent the development of the heart failure phenotype.17 Although these data support the hypothesis that impaired function of the SR is important in the progression to end-stage failure, these murine experiments do not establish whether increased expression of the SR Ca²⁺ ATPase can reverse heart failure once it has been established. The experiments performed by Maurice et al1 and del Monte et al2 suggest that this might be feasible in the intact human heart by using intracoronary adenovirus transfection of myocytes to increase the expression of SERCA2a.

This approach could face several potential problems, however. One is the question regarding whether increased expression of SR Ca²⁺ ATPase might produce arrhythmias due to increased SR Ca²⁺ loading. Ca²⁺ overload with an increased diastolic [Ca²⁺], produced by an increased Ca²⁺ influx (via the L-type Ca²⁺ channel or Na⁺/Ca²⁺ exchange), can produce delayed afterdepolarizations in the isolated cell, which will manifest as ventricular arrhythmias in the intact heart.18 It seems that in the murine heart, increased function of SR Ca²⁺ ATPase in vivo, which is induced directly by the increased expression of SERCA2a,19 does not increase Ca²⁺ influx via the L-type Ca channel or Na⁺/Ca²⁺ exchange, reduces diastolic [Ca²⁺], and does not induce arrhythmias. However, the degree of enhancement of SR function after adenoviral transfection of SERCA2a may be nonuniform in the intact heart. This could cause a nonuniformity of the [Ca²⁺] transient and a potential substrate for arrhythmias.

A second difficulty relates to the transient nature of adenoviral-transfected gene expression. Studies in which adenoviral vectors have been used to transfected genes into muscle cells have demonstrated that a cell-mediated immune response to the vector may limit expression to several weeks.1,20 Furthermore, humoral responses of neutralizing antibody to viral capsid proteins may prevent the readministration of the adenoviral vectors of the same type. Modifications of the adenovirus vector that may reduce host immune responses and the use of other viral vectors, such as the adeno-associated virus,20 may also be helpful in allowing a longer term, stable expression of transfected genes in the muscle tissue.

As previously discussed,9 it is possible that the impaired function of the SR produced by down-regulation of SR Ca²⁺ expression may itself promote hypertrophy and, thus, cause a vicious cycle of progression to failure. In some situations, up-regulation of the SR Ca²⁺ ATPase function by the techniques discussed above might stabilize or even improve cardiac function in vivo and, thus, provide a “molecular inotropic assist.” Because impaired SR Ca²⁺ ATPase function is undoubtedly not the only abnormality that contributes to contractile and electrophysiologic dysfunction in heart failure,15 better definition of the other factors involved and their potential for correction by genetic techniques are important for future investigation.

References


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