Response

I am gratified for the interest elicited by our study.1 With it, we did not mean to raise obstacles to laudable attempts to develop SERCA gene transfer modalities for the treatment of heart failure.2 Our laboratory has for a long time generated basic information, including the original description of cardiac SERCA,3 leading to the present interest regarding its role in heart failure. In our experiments, we use embryonic and neonatal hearts to obtain reliable myocyte cultures that are suited to quantitative and statistical measurements, including accurate determination of catalytic turnover in various isoforms.4 In these preparations, we showed sarcoplasmic reticulum development by confocal microscopy, and we did indeed find that a 2-fold increase in SERCA expression level improves Ca2+ signaling. This effect was demonstrated with complementary Ca2+ indicators to yield kinetic as well as stoichiometric measurements.5 We prefer not to culture adult myocytes because of their low survival rate, which precludes meaningful statistics on the effects of experimental perturbations on survival. An advantageous switch to the SERCA1 isoform has been demonstrated not only in our experiments but also in transgenic animals.6 It is important to recognize that, in transgenic animals, regulation by untranslated regions and occurrence of compensatory mechanisms allow safe levels of expression in surviving animals. Our concern is related to establishment of conditions for both safe and effective exogenous gene transfer by means of viral vectors, which is likely the method to be used in failing hearts. We have made careful efforts to restrict the viral titer to avoid cytotoxic effects1 and to use cell-specific promoters to limit expression to cardiac muscle.7 Certainly one would not want cytotoxic expression of exogenous SERCA in smooth muscle, endothelium, and even liver cells (in addition to cardiac myocytes), which would be obtained by nondiscriminative use of strong and constitutive promoters. We hope that this information will help the development of safe and effective methods of gene transfer.

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Letter to the Editor

Overwhelming Evidence of the Beneficial Effects of SERCA Gene Transfer in Heart Failure

To the Editor:

We read with great interest the work by O’Donnell et al1 on the possible toxic effect of the sarcoplasmic reticulum Ca2+ ATPase pump in neonatal cardiac myocytes. Because gene transfer of SERCA2a is being currently considered as a modality for the treatment of heart failure,2 the work by O’Donnell et al has the potential of raising concern about such a strategy. However, a number of limitations in this study preclude any definitive conclusions regarding the toxicity of overexpressing SERCA. The authors demonstrated the expression of the noncardiac isoform SERCA1 in embryonic and neonatal cardiac myocytes in their studies. These cardiomyocytes have a poorly developed sarcoplasmic reticulum and do not represent functionally the adult heart. In addition, the expression of the SERCA1 isoform may result in abnormal intracellular trafficking, which results in irregular calcium signaling. Although the authors state that cytotoxic effects observed with SERCA1 overexpression are “slightly” higher than with the empty or reporter viruses, no statistical significance is shown. The apoptosis index, which is unusually high in this study compared with other published studies,2 is not reportedly different between SERCA1 overexpression or GFP overexpression. The conclusions drawn in this study are in direct contrast to those validated by numerous experimental results showing that overexpression of the cardiac isoform, SERCA2a, improves contractility both in vivo and in vitro without detrimental effects.4–6 Most importantly, a recent study by Davia et al3 showed that overexpression of SERCA2a in adult rabbit cardiac myocytes has protective effects in contrast to β-agonism and prolongs survival in these adult cardiomyocytes. In addition, the exogenous expression of SERCA2a by either transgenesis or adenovirus has ranged from 1.13- to 2-fold,4,5 pointing toward an endogenous regulation of SERCA2a levels in cardiac cells. Although the study by O’Donnell et al4 describes cytotoxic effects of recombinant adenoviruses in embryonic and neonatal cardiac myocytes, there is very little evidence that exogenously increasing SR ATPase activity has detrimental effects. On the contrary, there are ample evidence that expression of the cardiac isoform, SERCA2a, not only rescues contractile function in failing hearts but has protective effects.

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