References


Intracellular [Ca2+] in Normal and Diseased Human Myocardium

Letter To the Editor

Beuckelmann et al recently published a report in *Circulation* showing that peak systolic intracellular calcium measured by fura-2 was diminished in single ventricular cells from patients with heart failure. Although the experimental findings were interesting, the suggestion by the authors that the major defect in contractile failure is a diminished intracellular calcium concentration was distressing. The authors propose that diminished calcium availability might explain impaired contractile performance in human heart failure because calcium concentration is intimately related to force production; it is important to note, however, that this conclusion is weakened by the fact that Beuckelmann et al did not measure force or cell shortening during excitation in their cells. These results are in contrast to those obtained by other investigators who used different experimental techniques and reported similar systolic calcium concentrations in myopathic and control human myocardium. More importantly, we and others have found similar force production in control and myopathic hearts, and it has been clearly demonstrated that in failing human myocardium, there is a significant increase in resting intracellular calcium concentration. The clinical extrapolation of the data proposed by the authors was especially alarming because they suggest that agents that increase intracellular calcium would be beneficial in patients with failure. Recently, however, the PROMISE trials have indicated that such agents may not be useful or may even be harmful to patients with failure. We feel that it is very important to alert the reader that the issue of whether intracellular calcium release is reduced during excitation-contraction coupling in heart failure is still controversial and that therapeutic decisions should not be based on this one report.

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References


Reply

We appreciate the comments by Dr. Morgan and Dr. Gwathmey concerning the interpretation of our data. There may have been some misunderstanding, however, as our results do not indicate a generally diminished intracellular [Ca2+] concentration. In fact, we have shown that resting [Ca2+] levels are increased in heart cells from patients with heart failure. Therefore, we completely agree that pharmacological agents that would simply increase resting [Ca2+] might be harmful. An increase in resting [Ca2+] might further reduce Ca2+ release from the sarcoplasmic reticulum through Ca2+-dependent inactivation of the Ca2+ release channel as shown by Fabiato. Therefore, in our paper we have put forward the idea that pharmacological agents that enhance Ca2+ uptake by the sarcoplasmic reticulum would be expected to be beneficial, which agrees with suggestions in earlier papers from Drs. Morgan and Gwathmey. Whether such a pharmacological intervention is beneficial in heart failure, of course, has to await a clinical trial.

Our data concerning the systolic [Ca2+] transient disagree with results from Dr. Gwathmey and her colleagues, and we have discussed possible reasons in our paper. [Ca2+] transients have not been measured in the papers by Movsesian et al. and by D'Agnolo et al. On the contrary, in their paper D'Agnolo et al showed an abnormal Ca2+ release from the sarcoplasmic reticum, which they proposed could lead to a diminished [Ca2+] transient. In the general review article on excitation-contraction coupling by Lederer et al, a single [Ca2+] record in a myocyte from a patient with heart failure is shown. In that paper, however, no quantitative comparison between diseased and undiseased myocardium has been attempted. Therefore, we think that the