

## EDITORIAL COMMENT

# Contractile Reserve: Are We Beginning to Understand It?\*

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The concept of contractile reserve is an old idea garnered from observations made by many investigators over the years. Various techniques have been used to study left ventricular (LV) performance in either the true failing heart or the heart with impaired systolic function, including post-systolic accentuation, epinephrine ventriculography, and various hemodynamic and echocardiographic responses to direct inotropic stimulation with dobutamine (1–3). The idea behind the test is to provide an objective means of determining the point at which the patient's heart has irreversibly failed. The identification of irredeemable heart damage could (for example) allow the physician to refer the patient for heart surgery or heart transplantation.

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In this issue of *JACC*, Kobayashi et al. (4) have further investigated the basis of diminishment in contractile reserve in 46 asymptomatic or mildly symptomatic patients with dilated cardiomyopathy. Patients were classified depending on their response of dP/dt max to dobutamine, as well as on the basis of their baseline ejection fraction. Plasma norepinephrine and myocardial [<sup>123</sup>I] metaiodobenzylguanidine scans were obtained, and an LV biopsy was done to characterize a number of molecular markers associated with the inotropic state. Patients less responsive to dobutamine demonstrated more abnormalities of sympathetic activity (higher plasma norepinephrine levels or less myocardial catecholamine tissue density) *despite a similarly reduced*

*ejection fraction*. These patients also had evidence for reduced molecular markers of LV contractile state, indirectly assessed by measuring messenger ribonucleic acid from LV biopsies. *This raises the possibility of using noninvasive imaging to characterize and possibly type subsets of intracellular abnormalities that underlie contractile dysfunction in the future.*

However, the longstanding and vexing question of what is driving the central theme of heart failure remains. Are the abnormal molecular markers a consequence of the impaired myocardial function, or are the molecular changes actually causing the decreased LV function? As the authors point out, markers such as myocardial tissue norepinephrine has long been known to be depleted in human failing hearts (5), and this is usually accompanied by increased plasma levels of norepinephrine (6). Likewise, numerous previous studies have demonstrated reduced beta-adrenergic receptors along with altered sarcoplasmic reticulum Ca<sup>2+</sup>-adenosine triphosphatase 2a (SERCA2a) and phospholamban in failing hearts (7). The fact that these changes were observed in relatively early stages of heart failure, and were more marked in those patients with reduced myocardial contractile reserve, would suggest that changes observed at the molecular level may actually be the cause of at least some of the impairment in LV function. Likewise, blocking the sympathetic nervous system at the beta-receptor level or replacing SERCA2a with gene therapy can reverse the reduced contractile state, thus fulfilling at least one of Koch's postulates.

Assuming that a more noninvasive approach to defining "contractile reserve" or some surrogate thereof in patients with heart failure is preferable, is there a need and a real benefit from such measurements? If so, what is the current status of such noninvasive approaches? Most cardiologists would like to know if there is such a point from which a

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return to more normalcy is either likely or not likely. Of course, this will always be a probability estimate, since no such test is likely to be precise in an individual patient. Moreover, for patients being considered for heart surgery, predicting which LV will recover depends to some extent on the quality of the operation in addition to the basal inotropic state of the LV before surgery. Nevertheless, such a need for defining “recoverability” seems self-evident. Two classic examples are patients with severe cardiomyopathy and severe regurgitant valvular disease, or patients with low gradient aortic stenosis and very poor LV function. This area needs much further study, and the study of Kobayashi et al. (4) is only a start in this direction.

In summary, estimating contractile reserve in patients with impaired LV function is worthwhile, particularly when making decisions about valve

surgery, coronary revascularization, and candidacy for heart transplantation. The basis for contractile reserve probably resides in several molecular markers of contractility, including beta-receptor density, altered SERCA2a, and phospholamban, as measured by myocardial biopsy by Kobayashi et al. (4). Imaging of molecular markers is on the horizon, but until it is more routine, cardiologists will continue to rely on those techniques that are performed in their own hospital laboratories with the most expertise and experience. For many, this will include the traditional assessment of contractile reserve.

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