Searching for the ideal inotropic agent to rescue a failing heart

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This editorial refers to ‘Beneficial effects of SR33805 in failing myocardium’ by Y. Ait Mou et al., pp. 412–419, this issue.

Heart failure (HF) is a major international public health problem that is becoming epidemic as the population ages.¹ Despite advances in treating HF in ambulatory patients, acute cardiac decompensation and failure remain associated with high rates of morbidity and death.¹ Acute and decompensated end-stage HF cause low cardiac output that can be treated with positive inotropic agents to increase myocardial contractility.² Conventional inotropic agents such as β-adrenergic agonists and phosphodiesterase inhibitors provide short-term haemodynamic improvement, but they do not improve prognosis.³,⁴ Such drugs increase cyclic AMP (cAMP) levels, which in turn increase intracellular Ca²⁺ levels and enhance contractility. Still, as high levels of intracellular Ca²⁺ are associated with increased energy consumption, arrhythmias, and myocardial cell death,⁵ these agents can worsen outcomes in HF patients.²,³ Consequently, novel strategies are needed to increase cardiac contractility and treat this debilitating illness.

A promising recent development is the unique class of positive inotropic agents known as ‘Ca²⁺ sensitzers’. These drugs act primarily by increasing the affinity of troponin C for Ca²⁺; they may also facilitate thin filament interaction and/or cross-bridge cycling.⁶ By increasing myofilament Ca²⁺ sensitivity, these drugs can, in theory, increase myocardial contraction without the risks associated with the increased intracellular [Ca²⁺] seen with traditional inotropes.⁶ Recent clinical studies suggest the Ca²⁺ sensitizer levosimendan may be useful for short-term inotropic support in various clinical settings.⁷ On the basis of these encouraging results, there is considerable interest in developing novel therapeutic agents that increase myofilament Ca²⁺ sensitivity to provide inotropic support in HF.

In this issue of Cardiovascular Research, Ait Mou et al.⁸ evaluate the beneficial effects of SR33805, a novel Ca²⁺ sensitizer, on in vivo and in vitro contractile properties of the failing heart. In a prior study in ventricular myocytes from non-failing hearts, they showed that SR33805 increased peak contractions but reduced the amplitudes of L-type Ca²⁺ currents and Ca²⁺ transients.⁹ They showed that the mechanism underlying the positive inotropic effect of SR33805 was an increase in myofilament Ca²⁺ sensitivity, in particular when cells were stretched.⁹ This combination of actions suggests that SR33805 may be an especially effective inotropic agent in the failing heart, where myocytes are subject to stretch and where diastolic Ca²⁺ levels are already high.⁷

In the current study, Ait Mou et al.⁸ evaluate the effects of SR33805 in the setting of heart disease. The author’s ligate the left coronary artery in rats to produce a myocardial infarction, which leads to HF after 18 weeks.¹⁰ They use echocardiography to show that an intraperitoneal injection of SR33805 improves cardiac contractile function in vivo in HF rats. They find that the decline in amplitude and slowed time course of contraction characteristic of failing myocytes are reversed by SR33805 (10 μM). Notably, and in contrast to currently used positive inotropes, the peak Ca²⁺ transient is not affected by SR33805, although it reverses the slowed decay of the Ca²⁺ transient seen in HF myocytes. This finding is unexpected, as in normal myocytes a lower concentration of SR33805 (0.1 μM) increases contractions but reduces peak Ca²⁺ transients and blocks Ca²⁺ currents.⁹ For this reason, the authors conclude that the cellular effects of SR33805 differ in control and failing myocytes.

What is the mechanism that underlies this increase in contraction with no change in intracellular [Ca²⁺] in HF myocytes? Ait Mou et al.⁸ find that SR33805 increases myofilament Ca²⁺ sensitivity in HF myocytes, especially at the long sarcomere lengths that would be expected in HF. What is more, they show that SR33805 increases myofilament Ca²⁺ sensitivity by inhibiting protein kinase A (PKA) activity and thereby reducing phosphorylation of troponin I. The authors conclude that SR33805 may reduce troponin I phosphorylation and help attenuate the hyperadrenergic state induced by HF.¹¹

Although the work of Ait Mou et al.⁸ highlights the importance of investigating drug actions under pathophysiological conditions, some questions remain. As the size of the Ca²⁺ transient is proportional to the magnitude of the L-type Ca²⁺ current,⁹ it is possible that SR33805 inhibits Ca²⁺ current in myocytes from normal but not failing hearts. Still, whether differences in the effect of SR33805 on Ca²⁺ transients can be explained by differential effects of the drug on Ca²⁺ current in normal vs. failing myocytes is an intriguing possibility that has not yet been investigated. If, as they suggest, SR33805 is a PKA inhibitor,⁸ it may affect other components of the excitation-
contraction pathway that are phosphorylated by PKA such as the L-type Ca\(^{2+}\) channel and the endogenous SERCA2a inhibitor, phospholamban.\(^{11}\) Inhibition of PKA by SR33805 may reduce phosphorylation of Ca\(^{2+}\) channels and thereby limit Ca\(^{2+}\) influx. On the other hand, less PKA-mediated phosphorylation of phospholamban would inhibit SERCA2a, so it would be difficult to explain how this drug actually accelerates Ca\(^{2+}\) transient decay in HF myocytes as seen in this study.\(^{8}\) As HF is characterized by abnormalities in excitation–contraction coupling at the myocyte level,\(^{9}\) it is difficult to predict the effects of drugs such as SR33805 on Ca\(^{2+}\) homeostasis in HF. Additional experiments to explore its impact on other Ca\(^{2+}\)-dependent regulatory components in myocytes from the failing heart could be rewarding.

The development of inotropic drugs that act on myofilament proteins is not limited to the Ca\(^{2+}\) sensitizers. Another new class of agents known as cardiac myosin activators target the kinetics of the myosin head to increase the rate of cross-bridge formation and increase myocyte contraction.\(^{12}\) Together with new positive inotropic agents like SR33805, drugs that target the myofilament proteins represent a promising new strategy in treating HF. The idea that cardiovascular diseases such as HF may influence drug action is important. As our group and others have shown, drugs affect cardiomyocyte electrical and contractile function differently in ischaemia and reperfusion than under normoxic conditions.\(^{13,14}\) Advanced age also affects Ca\(^{2+}\) homeostasis,\(^{15}\) which may modify drug actions; this may be particularly important in the coming HF epidemic.

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**References**