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Investigation of the cellular and molecular mechanisms of contractility in human ventricular cardiomyocytes

Cardiovascular disease is the leading cause of premature death worldwide. Coronary heart disease (CHD) is responsible for more than a half of Hungarian premature death, having CHD as the major contributor. Ichemia results in myocardial injury, and cell death and a decrease of myocardial contractility. In addition, a reperfusion injury characterized by ATP depletion, and increased intracellular Ca^{2+} concentrations. Many possible mechanisms have been proposed in the progression of cardiomyopathy. The most important are related to the increased oxidative and nitrosative stress related irreversible deterioration. One of the major mediator of myocardial cell death is related to the activation of poly(ADP-ribose)polymerase-1 (PARP-1). In general, PARP-1 acts as a molecular switch between apoptosis and necrosis. The regulation of intracellular Ca^{2+} concentration is important in the intracellular signaling and contraction and also in the survival of the cells upon ischemia-reperfusion. Increased intracellular Ca^{2+} concentration can activate a series of deleterious effects, including activation of protein kinase C (PKC) enzymes. There are controversial data regarding the role of PKC in the regulation of cardiac contractility, and only limited information is available about human physiology.

In summary, our study has clearly provided evidence of oxidative stress and PARP activation in human failing heart samples. Thus, the current study adds a further example of a human disease in which PARP activation has been demonstrated. Our data suggest that PKC plays a role in the maintenance of contractile force in human ventricular cardiomyocytes. The proposed mechanism of the PKC mediated protection is that PKCα translocates to the contractile protein machinery in a Ca^{2+} dependent manner, where it is anchored to the TnI. A practical application of these findings may be the pharmacological modulation of PKCα targeting in ischaemia/reperfusion to improve human cardiac contractility.

Keywords: PARP-1, PKCα, TnI, human cardiac contractility
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