Molecular mechanisms of diastolic dysfunction in diabetic cardiomyopathy

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The early stage of diabetes mellitus (DM)-related cardiomyopathy (DMCM) is characterized by left ventricular (LV) diastolic dysfunction. The aim of this study was to elucidate the mechanism of the defective Ca^{2+} signaling underlying diastolic dysfunction in DMCM. In the streptozotocin (STZ)-induced DMCM model mice 4 weeks after STZ treatment, diastolic function was impaired without reduction of ejection fraction. In the isolated LV myocytes from DM mice, the Ca^{2+} transient decay rate was slower than that from control. In the ventricle of DM mice, the expression level of junctophilin2 protein was significantly lower, although expression levels of $\text{Ca}_v1.2$, RyR2 and SERCA2 were the same as those of control mice, suggesting that uncoupling of dyad junction starts at the early stage. The phosphorylation level of phospholamban (p-PLN) was significantly lower. Insulin treatment recovered the p-PLN level and the relaxation rate of the isolated ventricular myocardium from DM mice. Furthermore, PKA-independent insulin/PKG signaling turned out to be required for maintaining basal p-PLN. These results indicate that the reduction of p-PLN caused by insulin signaling defect is responsible for the LV diastolic dysfunction in the early stage of DMCM.