Contribution of the loss of insulin signaling to diastolic dysfunction in the early onset of diabetic cardiomyopathy

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Left ventricular diastolic dysfunction is one of the earliest cardiac changes in the patients with diabetic cardiomyopathy (DMCM). Ca^{2+} signaling dysfunction has been shown to occur in human and animal models of DMCM. However, its molecular mechanism remains controversial. We aimed to elucidate the underlying mechanism of Ca^{2+} signaling defects in DMCM. In the type 1 diabetes mellitus (T1DM) model mice 4 weeks after injection of streptozotocin (STZ-4W), diastolic function was impaired without reduction of ejection fraction and ventricular fibrillation was not observed, which mimics the early stage of DMCM. In the ventricles of STZ-4W mice, the basal phosphorylation level of phospholamban-Ser^{16} (p-PLN) was significantly lower than that of control. Furthermore, the maintenance of basal p-PLN was found to require insulin signaling and the downstream NO/cGMP/PKG pathway in primary cultured neonatal mouse ventricular myocytes. Chronic insulin administration via sustained release implant restored the p-PLN level and diastolic function. These effects were not correlated with blood glucose level. These results indicate that the loss of cardiac insulin signaling in T1DM plays a crucial role in the impairment of Ca^{2+} cycling system and diastolic function in the early onset of DMCM.