

## MECHANISMS OF IMPAIRED CALCIUM HANDLING UNDERLYING DIASTOLIC DYSFUNCTION IN DIABETES.

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Diabetes has reached epidemic levels worldwide. Diastolic dysfunction is found in almost half of asymptomatic patients with well-controlled diabetes. However, the mechanisms that underlie diastolic dysfunction during diabetes are poorly understood. Our hypothesis is that, in streptozotocin-induced diabetic rats, diastolic dysfunction is associated with impaired myocardial calcium ( $\text{Ca}^{2+}$ ) signaling.

Echocardiographic examinations revealed relatively well-preserved systolic function in diabetic animals (mean  $\pm$  SE of fractional shortening:  $40.67 \pm 2.12$  and  $35.99 \pm 1.02\%$  at baseline and at 8 weeks of diabetes, respectively,  $P=\text{NS}$ ). However, Doppler flow imaging revealed diastolic dysfunction in the diabetic left ventricle: 1) the systolic/diastolic ratio and the duration of the atrial reversal wave of the pulmonary veins were significantly increased; 2) the velocities of the E and A waves were significantly decreased by 22 and 32%, respectively. In isolated ventricular myocytes, diabetes resulted in significant prolongation of the action potential duration compared to aged-matched controls (APD<sub>95</sub> increased by 80% at 2 Hz,  $P<0.05$ ), with occurrence of afterdepolarizations in 26.7% of diabetic myocytes, consistent with impaired  $\text{Ca}^{2+}$  homeostasis. Whereas there was no significant change in L-type Ca current, amplitude of  $[\text{Ca}^{2+}]_i$  induced  $\text{Ca}^{2+}$  fluorescent signal transients was reduced ( $P<0.05$ ) by 60%, with a significant prolongation of the transient decay in diabetic compared to age-matched control myocytes. SR  $\text{Ca}^{2+}$  load (estimated by measuring  $I_{\text{NCX}}$  and amplitudes of caffeine-evoked  $\text{Ca}^{2+}$  transients) was reduced ( $P<0.05$ ) by ~50% in diabetic myocytes. Amplitude and frequency of  $\text{Ca}^{2+}$  sparks were reduced ( $P<0.05$ ) by 34 and 20%, respectively, in diabetic compared to control saponin-permeabilized myocytes.

Using a model of diabetic cardiomyopathy with diastolic dysfunction, these findings suggest that *in vitro* impairment of  $\text{Ca}^{2+}$  reuptake during myocyte relaxation contributes to the observed *in vivo* diastolic dysfunction, and could provide novel therapeutic directions to improve diastolic function in the diabetic population.

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