Cellular mechanisms of STZ-induced diabetic cardiomyopathy

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Sustained diabetes mellitus leads to a deterioration of heart function, which occurs independently of the macro- and micro-vascular diseases. In humans, development of diabetic cardiomyopathy is associated with increased risk of heart failure, but our understanding of the cellular mechanisms underlying diabetic cardiomyopathy remain unclear. Myocardial Ca^{2+} homeostasis has been reported to be altered during diabetes, and is believed to be involved in the diabetes-induced primary cardiomyopathy (Dhalla *et al.*, 1982). As well, extracellular matrix changes have also been implicated (Cooper *et al.*, 2004). The aim of this study was to investigate Ca^{2+} homeostasis, myocardial contractility, and extracellular matrix remodeling in an animal model of diabetes, in order to gain insights into the mechanisms underlying diabetic heart disease.

ECG measurements from anaesthetized animals (halothane, flow rate 2 ml/min with 100% O_2) immediately prior to euthanasia and dissection of trabeculae showed that the normalized QT interval was prolonged in diabetic rats (STZ: 0.192 ± 0.004 s, (n = 18); Control: 0.177 ± 0.004 s, (n = 11)), as was action potential duration (AP_{90}) recorded from the LV free-wall of isolated, perfused, hearts (STZ: 0.195 ± 0.009 s (n = 7); Control: 0.136 ± 0.010 s (n = 6)). Simultaneous measurements were made of isometric force and intracellular calcium ($[Ca^{2+}]_i$, as the ratio of fura-2/AM fluorescence), in left-ventricular trabeculae from STZ, and their age-matched Controls under physiological conditions (37 °C, 5 Hz and pH 7.4). STZ-induced diabetic rats, 8 weeks post injection, had depressed cardiac contractility. Peak systolic stress was decreased in STZ (STZ: 10 ± 1 mN mm^{-2}; Control: 17 ± 2 mN mm^{-2}, n = 7 in each group), with slower time to peak stress (STZ: 77 ± 3 ms; Control: 67 ± 7 ms) and time to 90% relaxation of stress (STZ: 76 ± 7 ms; Control: 56 ± 3 ms). Histological studies of fixed LV free wall showed that the structure of the thin myofilament (f-actin) was disrupted in diabetic hearts, and the content reduced. Despite the obvious contractile dysfunction, no discernable difference was found in the amplitude of the Ca^{2+} transient in diabetic rats, although the time constant of Ca^{2+} transient decay was slower (STZ: 61 ± 3 ms; Control: 49 ± 3 ms). Western blot analysis of SERCA2a and Na^+/Ca^{2+} exchanger expression was carried out in LV tissue from 8 week post-injection animals. It was found that SERCA2a expression was reduced in diabetic hearts, without significant changes of Na^+/Ca^{2+} exchanger expression. SERCA2a is the major Ca^{2+} transport protein responsible for rapid removal of cytosolic Ca^{2+}, thereby allowing relaxation to occur.

In conclusion, both prolonged action potential duration, and decreased expression of SERCA2a can explain the slower kinetics of the Ca^{2+} transient in diabetic rats, whereas the reduced contractility is more likely to be associated with the changes in f-actin content and structure.

Dhalla, NS, Pierce GN, Panagia V, Singal PK, & Beamish RE. (1982) *Basic Research in Cardiology*, **77:** 117-139.

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