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Reduced myofilament calcium-sensitivity in diabetic human left ventricular cardiomyocytes.

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Background: The contractility of the diabetic heart is known to be diminished, but the mechanisms for this reduced contractility are not understood. We have found that cardiac β-adrenergic activation is unaffected by diabetes, and intracellular calcium regulating proteins (RyR, SERCA) are upregulated in human diabetic heart tissue, suggesting a mechanism other than intracellular calcium dysregulation compromises the contractility of the diabetic cardiomyocyte. Purpose: This study determined whether the calcium-sensitivity of myofilament contraction was reduced in skinned human left ventricular cardiomyocytes. Methods: After informed consent, left ventricular biopsies were obtained from open chest surgical patients who were categorized as non-diabetic with ejection fraction >50% (nDM-pEF; n = 5), non-diabetic with ejection fraction < 50% (nDM-rEF; n = 4) and diabetic with ejection fraction > 50% (DM-pEF; n = 4). Biopsied ventricular tissue was flash frozen in liquid N2 and stored at -80oC. For contractile measurements, single myocyte-sized preparations were obtained by mechanical disruption of this tissue in a Waring blender. The resulting suspension of intact myocytes, groups of myocytes and cell fragments was permeablized using 0.3% ultrapure Triton X-100. Permeablized myocyte preparations were attached between a capacitance-gauge transducer and a direct-current torque motor. Force (tension) was measured as a function of pCa (-log[Ca2+]) in the range of 9.0 to 4.5. For each activation steady force was allowed to develop, after which the cell was slackened and subsequently transferred to relaxing solution. Total force was measured as the difference between steady developed force and the baseline force immediately after the slack step. Active force was calculated by subtracting resting tension at pCa 9.0 from total force. Force at each pCa was expressed as a fraction of the maximum force (relative tension; measured in solution with pCa 4.5) obtained for that cell under the same conditions. PCa50, the calcium concentration at which 50% of maximal force was developed, was used to compare the calcium sensitivity of the two groups. Results: A total of 44 skinned cardiomyocytes preparations were tested (nDM-pEF =16, nDM-rEF = 13, DM-pEF = 15). PCa50 was lower (p < 0.05) in DM-pEF (5.71 ± 0.04) vs. nDM-pEF (5.94 ± 0.04) and nDM-rEF (5.84 ± 0.07) groups when compared as a mean value for each patient. When all cells were compared (not individual mean values) PCa50 in nDM-pEF (5.94 ± 0.06) > nDM-rEF (5.85 ± 0.03) > DM-pEF (5.71 ± 0.06). Conclusions: Myofilament calcium sensitivity was lower in left ventricular cells from patients with diabetes compared to non-diabetic groups. This may explain why contractility is reduced in these patients despite having normal β-adrenergic responsiveness and up-regulated cardiomyocytes calcium handling proteins.