High-intensity interval exercise attenuates cardiac remodelling in type-2 diabetes possibly through microRNAs restoration

Authors:
JKS Lew1, JT Pearson2, R Katare1, DO Schwenke1, 1University of Otago, Department of Physiology, HeartOtago, School of Biomedical Sciences - Dunedin - New Zealand, 2National Cerebral and Cardiovascular Center, Department of Cardiac Physiology - Osaka - Japan,

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Background
Diabetes induces pathological cardiac remodelling. These have been attributed to dysregulation of cardiac-specific microRNAs (miRs). Whether restoration of miRs could be a potential therapeutic strategy has not been fully addressed. High-intensity interval exercise (HIIE) appears to effectively attenuate cardiovascular complications in diabetes.

Purpose
The primary aim of this study was to assess the effect of HIIE on cardiac structure and associated cardiac-enriched miRs in db/db mice.

Methods
16-weeks old db/db mice with established cardiac dysfunction were subjected to either HIIE or no exercise. Age-matched non-diabetic db/+ mice with normal cardiac function were used as controls. Mice were subjected to exercise for 5 consecutive days a week for 8 weeks. Exercise protocol consisted of 10 bouts of 5 minutes run interspersed by 2 minutes of rest. Cardiac function was measured at baseline and endpoint using echocardiography. Heart tissues were harvested to assess cardiac remodelling by quantifying (i) fibrosis (ii) apoptosis (iii) cardiomyocyte regeneration using immunohistochemistry and their associated miRs: miR-133a, miR-499 and miR-222, respectively using real time-PCR. The protein expression of the respective miR’s direct target – CTGF, cleaved caspase-3 and p27 were assessed using western blot.

Results
At the end of 8 weeks study, diabetic developed systolic dysfunction (reduced fractional shortening and stroke volume) and down-regulation of cardiac-specific miRs -133a (5-fold decrease), an anti-fibrotic factor, and miR-499 (6-fold decrease), an anti-apoptotic factor, compared to the non-diabetic controls. The protein targets for both miRs – CTGF and cleaved caspase-3 levels were also markedly upregulated by 2.5-fold and 1.7-fold, respectively. These molecular changes were associated with augmented cardiac fibrosis (4-fold, p<0.0001) and apoptosis (5.5-fold, p<0.0001). Interestingly, cardiac dysfunction was normalized after 8 weeks of HIIE. HIIE restored the expression of both miR-133a and -499 to that comparable to non-diabetic mice, resulting in the normalization of both CTGF and caspase-3 protein levels. Exercise also markedly reduced collagen deposition (3-fold, p<0.0001) and apoptosis (2.8-fold, p<0.0001) in the diabetic myocardium. Importantly, HIIE increased the expression of cardiac miR-222, a pro-mitotic factor, by 10-fold (p<0.0001), resulting in 4.6-fold marked reduction of p27 level, a cellular senescence marker and direct target of miR-222. PCNA and MHC-beta double positive stained cardiomyocytes in immunohistochemistry confirmed a 2.4% (p<0.01) increase of cardiomyocytes proliferation in diabetes.

Conclusion
HIIE attenuated cardiac fibrosis, apoptosis and cardiomyocytes proliferative properties in diabetes, contributing
to improved cardiac function. These functional changes might occur in part due to the restoration of cardiac miR-133a, 499 and -222 and their respective target proteins.