Modulation of myocardial inflammation, fibrosis development and ventricular arrhythmogenicity by endurance exercise in murine coxsackievirus B3 myocarditis

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Aims: Nonischaemic myocardial fibrosis is associated with progressive deterioration of myocardial function and forms the substrate for arrhythmias in atria and ventricles. In the absence of a specific aetiology, its origin is commonly attributed to preceding viral myocarditis. Athletes presenting with ventricular arrhythmias often demonstrate nonischaemic fibrosis on magnetic resonance imaging. Previous translational studies have shown an adverse effect of exercise on the course of acute viral myocarditis. Nevertheless, the effect on myocardial fibrosis development, a frequent and important consequence of viral myocarditis, has not yet been investigated. In the present study, we evaluate for the first time the impact of endurance exercise on longer-term myocardial inflammation, myocardial fibrosis and arrhythmogenicity using a murine viral myocarditis model.

Methods and results: Male C57BL/6J mice (11 weeks of age, n=72) were randomly assigned to 8 weeks of treadmill running (EEX) or without exercise (SED). Two weeks into the study (training or control), animals were injected intraperitoneally with either coxsackievirus B3 to induce acute viral myocarditis (CVB) or vehicle (PBS). Exercising myocarditis mice showed lower mortality (11\% vs. 27\%), albeit without statistical significance (P=0.23). At sacrifice (i.e. 6 weeks after inoculation), prominent myocardial inflammatory infiltration and cardiomyocyte loss was observed in both CVB groups, without difference on semiquantitative histological scoring. Nevertheless, the infiltrating cells in the CVB-EEX group were more often proinflammatory in nature (predominantly iNOS-reactive macrophages and positive CD8+/CD4+ ratio) compared to these in CVB-SED (predominantly arginase-1-reactive macrophages and higher CD4+/CD8+ ratio). In addition, the EEX group showed more haemosiderin-laden macrophages and spindled fibroblasts as signs of organisation. At that time, the majority of virus was cleared from the heart. Treadmill running during myocarditis enhanced development of interstitial fibrosis (with limited or extensive distribution)(82.4\% in CVB-EEX vs. 56.3\% in CVB-SED; P=0.049) and perivascular and/or interstitial fibrosis with extensive distribution (64.7\% & 64.7\% in CVB-EEX vs. 50\% & 31.3\% in CVB-SED; P=0.048). The highest scar counts were observed in CVB-EEX, but the mean count (1.9 vs. 1.2; P=0.19) did not significantly differ between the myocarditis groups. In CVB-EEX, the lesions contained denser and more organised collagen bundles. In vivo electrophysiology studies showed similar ventricular arrhythmia inducibility (P>0.20) and arrhythmia burden (P=0.49) in the myocarditis groups, although the longest arrhythmias and highest cumulative burden occurred in CVB-EEX.

Conclusion: Endurance exercise training during viral myocarditis modulates the longer-term inflammatory process and promotes perivascular and interstitial fibrosis development, potentially enhancing ventricular arrhythmogenicity.