Exercise training reduces ventricular arrhythmias through restoring calcium handling and sympathetic tone in myocardial infarction mice

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学位論文題目	Exercise training reduces ventricular arrhythmias through restoring calcium handling and sympathetic tone in myocardial infarction mice（運動トレーニングは心筋梗塞マウスにおけるカルシウム制御と交感神経緊張を回復することにより心室性不整脈を抑制する）

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Abstract of thesis

（Purpose）Despite important advances in drug and device therapy, myocardial infarction (MI) remains a leading cause of death. During the pathophysiological progress, the malignant arrhythmias such as ventricular tachyarrhythmias have a great impact on mortality, associating with the imbalance of autonomic nervous system (ANS). β-adrenergic receptor blocker (β-blocker) has been established as a first-line medication for heart failure patients.

Exercise training is considered an effective non-pharmacological treatment for cardiovascular diseases. According to guidelines for heart failure, cardiac rehabilitation (CR) programs have been given a Class I recommendation for cardiac patients, with exercise therapy consistently identified as a central element.

Different mechanisms of improved outcomes of exercise have been reported, such as enhancing contractility, attenuating left ventricle (LV) remodeling and decreasing ventricular arrhythmias. However, some studies showed conflicted results, especially on intensive exercise after MI. Moreover, it remains to be fully elucidated what are the cellular/molecular mechanisms.

In this study, the author aimed at investigating the effects and mechanisms by intensive exercise training in post-MI mice, especially anti-arrhythmic potential, via comparing the effects of exercise versus an established first-line medicine β-blocker treatment.

（Materials and Methods）Wild-type male mice underwent sham-operation or permanent left coronary artery ligation to induce MI. MI mice were divided into a sedentary (MI-Sed) and two intervention groups: exercise training (MI-Ex) and β-blocker treatment (MI-βb). MI-Ex animals underwent 6-week treadmill training, while MI-βb animals received oral bisoprolol without exercise. Cardiac function and structure were assessed by echocardiography and histology. Oxygen consumption at peak exercise (peak VO_2) reflects maximal cardiac output during exercise and is measured for evaluating exercise tolerance and cardiopulmonary function. The incidence of spontaneous ventricular arrhythmia was evaluated by telemetry recording, and ANS function was evaluated by heart rate variability (HRV) analysis. mRNA and protein expression in the LVs were investigated by real-time PCR and Western blotting.

（Results）The author concluded that there were no differences in survival rate, MI size, and echocardiographic findings between MI groups. Compared with MI-Sed, MI-Ex and MI-βb showed decreased sympathetic tone and lower incidence of spontaneous ventricular arrhythmia. The elevated mRNA expressions of brain natriuretic peptide (BNP) and miR-1 in MI-Sed were decreased in MI-Ex and MI-βb. By Western blot, the author showed that the hyperphosphorylation of CaMKII and RyR_2 were restored by exercise and β-blocker treatment. Furthermore, the suppressed expression of PP2A, an miR-1 target and a major phosphatase in the dephosphorylation of CaMKII and RyR_2, was also recovered by exercise and β-blocker treatment.

（Discussion）In the present study, the author we found that chronic intensive exercise training improved the imbalance of sympathetic and parasympathetic activities, reduced the incidence of VT, and restored calcium handling in MI mice, despite no obvious improvement in cardiac structure or function. Thus, exercise training in the subacute to chronic phase of MI did not increase the risk of malignant arrhythmias, but rather restores autonomic function and cardiac electrical stability.

Although both exercise and treatment with β-blockers did not improve the MI area or cardiac systolic function, the author found that exercise training significantly improved peak VO_2. This finding is consistent with the previous observation that exercise has a better effect on cardiopulmonary function and exercise capacity.

The author showed that phosphorylated CaMKII and Ser2814-phosphorylated RyR_2 were significantly increased in the MI-Sed group compared with sham animals, but which were suppressed in the MI-Ex group. The author, thus, speculated that inhibition of CaMKII dependent-RyR_2 hyperphosphorylation by chronic exercise training may be a key mechanism underlying the suppression of ventricular arrhythmias in heart failure after MI. In the present study, we showed that elevated miR-1 expression and decreased PP2A activity in MI was significantly restored by chronic exercise training and β-blocker treatment. These findings suggest that the antiarrhythmic effects of chronic exercise or β-blocker treatment are, at least in part, related to regulation of miR-1 expression, and downstream phosphatase activity of calcium handling-related molecules, in cardiomyocytes.

Abstract of assessment result

（General Comments）

The author’s thesis revealed that continuous intensive exercise training can suppress ventricular arrhythmias in the subacute to chronic phase of MI, through restoring the hyperphosphorylated CaMKII-RyR2 pathway and autonomic imbalance, similar to that for β-blockers. Thus, exercise may be a safe and effective therapy for improving outcome in heart failure patients after MI.

The author’s research contributes to the improvement of the prognosis of heart failure patients after MI by intensive exercise training, and is highly evaluable.

（Assessment）

The final examination committee conducted a meeting as a final examination on January 15 2019, in the presence of all members. The author provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

（Conclusion）

The final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Medical Sciences.