Voluntary Exercise Preserves Cardiac Function in DCM Model Mice

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Background: Dilated cardiomyopathy (DCM) is one of major causes of heart failure (HF), characterized by ventricular dilatation and contractile dysfunction. In addition to HF, about 30-40% of patients with DCM die from premature death with lethal arrhythmia. To date, the exercise is considered to be one of therapy for HF as shown in the guideline for chronic HF (Japanese Society of Cardiology in 2010). However, the effects of exercise on DCM patients are still unclear, because evaluation of exercise therapy in DCM patients is associated with risks of worsening of HF or sudden cardiac death. Investigations with animal models of inherited DCM are necessary. Previously, we have established the method to evaluate the severity of HF using a mouse model of DCM (Sugihara et al. PLoS One, 2013). In the course of these studies, we found that voluntary exercise started at young age significantly prolongs survival rate of DCM mice. In this study, we investigated the effects of voluntary exercise on the cardiac function and arrhythmogeneity in DCM model mice.

Methods: We used a knock-in mouse model having one of human inherited DCM mutation, TNNT2 ΔK210, which decreases Ca2+ sensitivity of myofilaments (Du et al. Circ Res, 2007). Homozygous ΔK210 (below are called DCM mice) and wild type (WT) mice at 1 month-old were housed with a running wheel (diameter = 12 cm) every 48 hours or all day long, and daily voluntary running activity was recorded. At 2 month–old, end-diastolic dimension and ejection fraction (EF) were measured by echocardiography. Heart, lung and lower extremity muscle (soleus, plantaris and gastrocnemius muscles) were excised and their weights were measured together with body weight. Gene expressions of major ion channels (Kv1.5, Kv4.2, KChIP2, Nav1.5, Cav1.2, etc.,) were quantified by real time PCR analysis.

Results and Discussion: DCM mice died with t1/2 of approximately 70 days as reported previously (Du et al., 2007). The average lifespan of the DCM mice who continued running exercise every 48 hours was about 20 days longer than that without exercise. Moreover, systolic cardiac function defined by the average EF was higher in DCM mice with exercise than in those without exercise [0.47 ± 0.10 (n=7) vs. 0.31 ± 0.10 (n=4), p<0.05] at 3 month–old. On the other hand, electrical remodeling such as down–regulation of multiple types of K+ channels and accessory subunits has been reported in the DCM mice and closely related to the arrhythmogeneity in them (Suzuki et al. PLoS One, 2012). Some of these expression in DCM mice starting exercise at young age were relatively preserved (n=6). We further discuss the relationship between cardiac function, electrical remodeling and leg muscle weights as a measure of exercise intensity.

Key words: voluntary exercise, heart failure, lethal arrhythmia, dilated cardiomyopathy

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