Abstract: **P629**

**Voluntary exercise associated with myokine production ameliorates cardiac remodeling and inflammation in a myocardial infarction mouse model**

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Background: Left ventricular (LV) remodeling, through excessive inflammation, leads to heart failure. Exercise (Ex) training is associated with a risk reduction in heart failure through direct and indirect mechanisms by which Ex contributes an anti-inflammatory effect. During Ex, contracting muscle fibers release myokines, including interleukins (ILs), tumor necrosis factor α (TNF-α), follistatin-like protein 1 (FSTL-1), and fibroblast growth factor 21 (FGF-21), into the bloodstream. These myokines may have beneficial effects on other damaged organs, such as an infarcted myocardium, through anti-inflammatory effects. However, the exact mechanisms of the anti-inflammatory effects of voluntary Ex in myocardial infarction (MI) are poorly understood. Therefore, we investigated the effect of voluntary Ex on cardiac remodeling and inflammation, the relationship between cardiac remodeling and skeletal muscle (SKM) response, and circulating myokine levels in a mouse model of MI.

Methods: Twelve-week-old male C57BL/6J mice were used and divided into the following 4 groups: sham operation (Sham), MI, Sham+Ex, and MI+Ex. MI was induced by ligation of the left anterior descending coronary artery. Ex groups began voluntary wheel running for 4 weeks after the operation. An echocardiography was performed at baseline and 4 weeks after the operation. The mRNA levels in the LV infarcted area and SKM were measured with RT-PCR and western blot analysis. Plasma levels of myokines were also measured with immunoassays.

Results: Four weeks after MI induction, echocardiographic evaluation showed that the MI mice had a larger LV end-diastolic diameter (LVEDD) and end-systolic diameter (LVESD) than the Sham mice. The MI mice also showed higher mRNA levels of TNF-α, IL-1β, IL-6, and IL-10 in the LV tissue when compared to the Sham mice. These changes were significantly ameliorated in the MI+Ex mice. Interestingly, in the MI+Ex mice, mRNA levels of IL-6, IL-1β, FSTL-1, and FGF-21 in the SKM were significantly higher than in the MI mice, while there were no significant differences in TNF-α and IL-10 levels in all groups. Similarly, protein expression levels of peroxisome proliferator-activated receptor gamma coactivator 1-alpha, sirtuin-1, and mitochondrial transcriptional factor A of mitochondrial function markers in SKM were also significantly higher in the MI+Ex mice than in the MI mice. Furthermore, there were significant correlations between plasma levels of IL-1β, but not other myokines, and LVEDD, and LVESD. In addition, there was also a significant correlation between the SKM IL-1β level and LVESD in the Sham+Ex mice (all, P<0.05).

Conclusions: Amelioration of cardiac remodeling and inflammation by voluntary Ex is associated with increased myokines, especially IL-1β, in a MI mouse model. These results suggest that increased myokine levels, through voluntary exercise, may play an important role in the prevention of cardiac remodeling after MI.