Proper exercise intensity is distinctly beneficial to human health. Notably, along with healthy eating habits and smoking cessation, physical activity plays a beneficial role in the prevention of cardiovascular diseases. Exercise lowers blood pressure, body weight, and stress, thereby reducing susceptibility to cardiovascular disorders. The combination of aerobic workouts and strength training helps strengthen skeletal muscles, which reduces demand on the heart by improving the ability of muscles to draw oxygen from the blood. Furthermore, exercise has curative properties against diabetes, one of the most critical risk factors for cardiovascular disease. However, excessive exercise has detrimental effects on the myocardium. Specifically, exhaustive exercise training may cause cardiac injury, including ischemic heart disease, heart failure, and lethal arrhythmia, which results in sudden cardiac death. Thus, exercise training is a double-edged sword.

Increasing lines of evidence suggest that repeated transient ischemia, termed ischemic preconditioning (IP), has a protective role in the myocardium against a subsequent sustained ischemic event. Previous investigations demonstrated that IP induces cardioprotective effects by increasing myocardial tolerance to ischemia-reperfusion (I/R) injury, thereby alleviating cardiac dysfunction. As is the case in IP prior to myocardial ischemia, exercise preconditioning (EP), brief episodic regular exercises performed prior to excessive exercise, effectively reduces myocardial damage in response to exhaustive exercise. 1 EP contains a biphasic protection manner, namely a short-lived early phase and a long-lived late phase. The short-lived early phase occurs immediately after exercise, while the long-lived late phase develops 24 hours post-exercise. Indeed, similar to the case in IP, EP has the potential to improve myocardial tolerance to I/R injury, thereby enhancing cardiac function. Previous investigations demonstrated the salutary effect of EP against exhaustive-exercise-induced cardiac injury. Hao, et al. previously demonstrated that protein kinase Cε (PKCε) plays a critical role in EP-mediated myocardial protection in response to exhaustive-exercise-induced myocardial injury. 2 However, the detailed mechanism by which EP protects the myocardium has yet to be established.

In this issue of International Heart Journal, Lu, et al. revealed that the EP-mediated modulation of K_{ATP} channel expression and autophagy machinery alleviates exhaustive-exercise-induced myocardial damage. 3 The myocardial K_{ATP} channel consists of pore-forming Kir6.2 and regulatory SUR2A subunits. A growing body of evidence suggests that the K_{ATP} channel plays a critical role in protecting the myocardium against myocardial infarction by promoting IP. Indeed, previous investigations demonstrated that K_{ATP} channel openers such as nicorandil exert cardioprotective effects in response to ischemia. 4 On the other hand, excess upregulation of the K_{ATP} channel causes detrimental effects in myocardial ischemia. The expression levels of the Kir6.2 and SUR2A subunits are upregulated during I/R, thereby contributing to the susceptibility of lethal ventricular arrhythmias in response to I/R injury. 5 Consistent with these results, Lu, et al. demonstrated that the upregulation of K_{ATP} channels is accompanied by exhaustive-exercise-mediated acute myocardial injury. 3 They also observed that EP antecedent to exhaustive exercise markedly reduced Kir6.2 and SUR2A protein expressions. Furthermore, they found that the influence of EP on the SUR2A expression level is more significant than that for Kir6.2. Taken together, the results from Lu, et al. suggest that opening of the cardiac K_{ATP} channels is protective, whereas overexpression of K_{ATP} channel subunits might be detrimental to the myocardium in response to exhaustive exercise, which could be alleviated by EP through the downregulation of SUR2A expression. 6

Autophagy is an evolutionally conserved catabolic process in which proteins and organelles are degraded in lysosomes. 7 Autophagy functions as a keeper of cellular homeostasis by eliminating intracellular waste and dangerous objects such as aggregated/denatured proteins and damaged organelles in the basal condition. Autophagy also plays crucial roles in the adaptation to a wide variety of stresses in various cells. Indeed, previous investigations demonstrated that appropriate exercise induces autophagy,
The relationship between exercise intensity and the cardiac homeostasis maintenance system, including K<sub>ATP</sub> channels and autophagy, Lu, et al. now provide evidence that exhaustive exercise dysregulates cardiac K<sub>ATP</sub> channels and autophagy. A: Under basal conditions, both K<sub>ATP</sub> channels and autophagy play beneficial roles in maintaining cardiac homeostasis. B: Exhaustive exercise induces cardiac K<sub>ATP</sub> channel overexpression and excessive autophagy activation, thereby aggravating cardiac injury. Such detrimental effects could be attenuated by exercise preconditioning.

Although this study provides answers to several unsolved questions raised in previous investigations, a number of issues persist. The first is the lack of solid evidence raised by the animal experimental model. To resolve this concern, the effect of K<sub>ATP</sub> channel blockers in the heart in response to exhaustive exercise should be investigated. Second, the molecular mechanism by which excessive K<sub>ATP</sub> channel subunit expression aggravates myocardial damage in response to exhaustive exercise is unknown. Third, debate persists about whether the activation of autophagy in response to cardiac injury is harmful. Therefore, more robust data are needed to substantiate the findings the authors demonstrated. To resolve this concern, it would be better to conduct a line of in vivo experiments on autophagy machinery using genetic loss-of-function models. It also remains unclear whether there is an association between K<sub>ATP</sub> channels and autophagy activity in the process of exhaustive exercise-induced myocardial injury. If these concerns are resolved, these findings could form a solid theoretical background in which EP precedent to exhaustive exercise training is mandatory to avoid severe myocardial damage.

Disclosures
Conflicts of interest: None.

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