Letter to the Editor

Exercise Does Not Protect the Female Heart: An Unconvincing Conclusion?

To the Editor:

The recent article by Paroo et al1 addressed an important issue relating to the sex difference in exercise-induced late cardioprotection against ischemia-reperfusion (I-R) injury. This study prompts a few concerns that I would like to share with the Editors and the readers of Circulation Research.

(1) Exercise-induced cardioprotection in females. In this study, Paroo et al1 reported a rather provocative finding showing no exercise-induced cardioprotection in female rats compared with males, which challenges the common sense that moderate exercise could benefit both males and females in reducing cardiovascular risk factors and improving postinfarct heart function and survival. Unfortunately, these authors ignored the fact that a number of studies by several research groups have independently demonstrated the sex selectivity as well as the alternative end effector(s) of exercise-induced cardioprotection against I-R injury in female rats.2–4 In particular, there is an obvious discrepancy between their experimental data and those of Ji et al,2 Taylor et al,3 and Hamilton et al,4 who were able to find enhanced posts ischemic ventricular contractile function in female rats after exercise training.

(2) Hsp70 as the primary determinant in delayed cardioprotection. Contrary to what Paroo et al1 concluded on the critical role of Hsp70, the above-mentioned studies in female rats3–4 suggested that exercise-induced cardioprotection is not dependent on Hsp70, given that exercise under either cold or warm environment resulted in similar cardiac resistance to I-R despite the blunted Hsp70 induction in the cold group compared with the warm group. In addition, recent studies from our group5–8 and many others9–11 showed that Hsp70 is unlikely to be the primary determinant of late cardioprotection induced by whole-body hyperthermia, another strong inducer of heat shock proteins comparable to exercise. Our argument is based on the fact that the time course of hyperthermia-induced cardioprotection did not match that of cardiac Hsp70 or Hsp27 protein expression after heat stress.6,9,11 In some cases, a significant induction of Hsp70 did not lead to an anticipated cardioprotection.7,10 Furthermore, the inhibitory effect of estrogen on exercise-induced cardiac Hsp70 reported by Paroo et al1 conceptually contrasts a recent study by Lu et al12 showing that 17-β-estradiol induces heat shock proteins in brain arteries and potentiates the heat shock protein induction by ischemia in glia and neurons.

(3) Ventricular developed pressure as end point of cardioprotection. Another weakness of the study is that the authors used only ventricular developed/end-diastolic pressure as the end point to assess I-R injury. Although the authors mentioned the use of creatine kinase (CK) leakage as an index of cell membrane integrity, they did not provide any details or statistics on the CK results. No other measurements (eg, infarct size) were performed to determine the necrotic and/or apoptotic cell death after I-R. Relying solely on a functional end point could be problematic because a recent study by Gelpi et al13 suggested that posts ischemic ventricular developed pressure may be an unreliable marker of tissue salvage and is highly species dependent due to various levels of xanthine oxidase among species, which may differentially affect the purine-related stunning.

In brief, further investigations targeted to multiple end points of cardiac I-R injury in various animal species are needed to confirm the sex selectivity as well as the alternative end effector(s) of exercise-induced cardioprotection, eg, antioxidants2–4,14 and nitric oxide synthases.5,15,16 Unless such pieces of solid evidence become available, the conclusions made by Paroo et al1 remain unconvincing.
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