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EDITORIAL COMMENT

Exercise at the Extremes

Unraveling the Mechanisms of Deleterious Cardiovascular Adaptations*

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The cardiovascular benefits of exercise are great, as regular exercise training improves risk factors and active individuals experience a 20%-50% risk reduction in cardiovascular morbidity and mortality. The dose-response association between exercise volumes and cardiovascular health benefits appears to be curvilinear, with the greatest health improvements with small amounts of exercise and greater risk reductions with higher exercise volumes. Such observations have contributed to the belief that "more exercise is better." There is emerging evidence, however, that extreme exercise, characterized by long-term, high-volume, high-intensity training, may induce deleterious cardiovascular adaptations in some individuals. For example, intensive exercise training has been associated with an increased prevalence of coronary atherosclerosis, myocardial fibrosis, atrial fibrillation, and aortic dilatation. These findings indicate a possible upper limit for the health benefits of exercise.

To allow early identification of individuals at risk and promote the development of preventive countermeasures, insight into the underlying mechanisms of exercise-induced cardiovascular maladaptations is key. Unfortunately, it is impossible to conduct a randomized clinical trial to evaluate the cardiovascular benefits and possible risks of long-term exercise training because of the following: 1) the sample size and study duration (≥10 years) required to document deleterious effects is simply too large; 2) compliance with assignment to active or low, moderately, or highly active groups would be difficult and unethical to enforce; and 3) the cost of such a study would be enormous. Animal models are, therefore, a good alternative to investigate how exercise can produce deleterious cardiovascular adaptations.

In this issue of *JACC: Basic to Translational Science*, Rubies et al[1] studied the consequences of long-term moderate vs intense exercise on the vasculature in a rodent model, and aimed to uncover mechanisms responsible for these adaptations. For this purpose, 78 male Wistar rats were randomly assigned to a long-term exercise group or a sedentary control group (n = 27). Exercised rats were subjected to a moderate exercise (45 min/session at 35 cm/s; n = 28) or intensive exercise (60 minutes at 60 cm/s; n = 23) training program with 5 exercise sessions/wk for 16 weeks, which is estimated to equal a 10- to 12-year training period in humans. A comprehensive combination of in vivo, ex vivo, and in vitro measurements was conducted to assess functional and structural properties of the thoracic aorta, left carotid artery, and intramyocardial arteries.

A larger aortic root, stiffer thoracic aorta, and increased fibrosis in the carotid artery and thoracic aorta were found in the intensively trained rats. Furthermore, intensive exercise was associated with an increased wall to lumen ratio, stiffening, and elastic laminae abnormalities of intramyocardial arteries. Endothelial function improved after both training regimes, although intensive exercise seemed to affect NO production more. Moreover, microRNA analyses indicated that deregulation of microRNAs miR-132-3p, miR-212-3p, miR-146b-5p, miR-326-5p, and ACE-1 were associated with adverse vascular remodeling. Vascular changes persisted after 4 weeks

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detraining. The authors are to be congratulated on this timely, very elaborate study in which a combination of state-of-the-art measurement techniques was adopted.

A key observation of this study was the impact of intensive exercise on the tunica media. The higher degree of fibrosis suggests that the tunica media is affected by exercise-induced metabolic changes and/or smooth muscle damage, as indicated by increased smooth muscle cell stiffness, and may be vulnerable to the development of atherosclerosis. These findings fit with our previous hypothesis that coronary calcification in athletes may be primarily located in the tunica media.[2] Intimal and medial calcification have different causal pathways and associated cardiovascular risks. Medial calcification is related to vascular aging and metabolic shifts secondary to diseases and vascular stiffening, whereas atherosclerosis is located in the intimal layer. Contemporary computed tomography imaging has insufficient resolution to discriminate between medial vs intimal calcification, so findings from this animal study with ex vivo histology provide important directions for follow-up studies.

Only few markers of atherosclerosis were assessed within the present study. Calcification scores were not available, and structural and functional properties were only assessed of intramyocardial arteries but not of epicardial coronary arteries, which are assessed in most human studies. This may complicate the translation of findings, especially because intramyocardial arteries are free from atherosclerosis in humans.[3] Furthermore, rodents are known to be atherosclerosis-resistant, so healthy young rats may not be the best model to investigate coronary atherosclerosis.

The impact of exercise on the aorta was also assessed. The larger aortic root in the intensive exercise group fits with recent observations in humans, as >20% of lifelong master athletes had larger aortic dimensions compared with normograms.[4] The prospective and randomized nature of the present study further supports a causal association between exercise and aortic root dilatation, whereas the presence of increased stiffening and fibrosis highlights additional deleterious adaptations. However, CD68+-immunostained aortic sections revealed lower density of macrophage and monocyte presence and a better endothelial function of trained vs sedentary rats, indicating a lower risk of peripheral atherosclerosis following exercise training. These findings align with recent observations that the association between exercise and atherosclerosis is different for cardiac vs noncardiac arteries, with a lower risk of thoracic aorta calcification with increasing exercise volumes.[5]

The clinical implications of the present study remain unclear. Although various deleterious vascular adaptations were observed in intensely trained rats, it was not assessed whether they were related to clinical outcomes such as major adverse cardiovascular events or (cardiovascular) mortality. Future prospective studies, preferably in recreational athletes, are therefore warranted. Such studies should also untangle the differential deleterious effects of exercise volume vs intensity, because both exercise characteristics (volume: 60 min/session vs 45 min/session, intensity: 60 cm/s vs 35 cm/s) were increased in the intensive vs moderate exercise group, although it has been suggested that a higher intensity rather than an increasing exercise volume may be the main substrate for deleterious cardiovascular adaptations. In this regard, it is also unknown whether the combination of a higher intensity and volume in the intensive vs moderate exercise group may have resulted in more electrical shocks to stimulate running, which might confound some of the findings.

Our understanding of the underlying mechanisms of exercise-induced deleterious cardiovascular adaptations is still incomplete. The study of Rubies et al[1] adds an important piece to the puzzle, because they reported that intense exercise induced tunica media fibrosis along with dilatation and stiffening of the aorta. Their animal model provides exciting possibilities to study other cardiac maladaptations, including exercise-induced cardiac troponin release, myocardial fibrosis, and arrhythmogenic cardiomyopathy. Such studies are eagerly anticipated because they advance our knowledge on the potential side effects of extreme exercise, which is needed to allow early identification of individuals at risk and to provide the maximal benefits from exercise as a medicine.

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