Marathon Rat
Myocardial Remodeling in an Animal Model of Vigorous Endurance Exercise and Implications for Humans

Paul G.A. Volders, MD, PhD

Cardiac adaptation to intensive exercise has long intrigued cardiologists and physiologists, particularly in relation to the notion that different types of exercise drive divergent remodeling. On the basis of a meta-analysis of 59 echocardiographic studies (including 1451 male athletes 18 to 40 years of age), Pluim et al concluded that endurance-trained runners, who are known to develop eccentric cardiac hypertrophy, demonstrated a more pronounced left ventricular (LV) wall thickening than expected. Strength-trained athletes showed an unanticipated increase in LV internal diameter whereas concentric cardiac hypertrophy. These adaptations accounted for a higher LV mass, whereas no differences were found between athletes and nonathletes regarding LV ejection fraction, fractional shortening, and early and late ventricular filling velocity ratio. Recently, Pelliccia and colleagues reported on a longitudinal assessment in young Olympic athletes engaged in rowing, canoeing, cycling, middle- and long-distance running, cross-country skiing, swimming, or participating in triathlons. The investigators concluded that extreme endurance training over long stretches of time (4 to 17 years) was not associated with significant changes in LV shape and function or the occurrence of cardiovascular symptoms and events. However, this unique study has been criticized for including only athletes who had undergone mandatory cardiovascular screening before enrollment, so those already having exercise-induced cardiac abnormalities would have been excluded. A second criticism was that no analysis of the right ventricle (RV) was performed, although extreme exercise can cause RV dysfunction and arrhythmias. Generally, the risk of primary cardiac arrest is increased among men with infrequent vigorous exercise, whereas, for those exercising habitually, the overall risk is decreased. There is a striking male predominance of sudden death among athletes.

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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What happens with the RV and the atria during long-term intensive sports training? Previous data indicated disproportional changes in the RV and LV by extreme exertion, with a transient reduction in RV function and the release of cardiac biomarkers (brain natriuretic peptide, troponin I) in the acute stage. It is currently unknown whether, and to what extent, these early changes relate to chronic adaptation. In athletes training 9 to 18 h/wk and in elite athletes training even more, end-diastolic dimensions of both the LV and RV were significantly larger than in age-matched control subjects, confirming earlier results. In the elite athletes with extreme exercise, RV dilatation appeared more prominent than LV enlargement, but despite increased end-diastolic and systolic areas, the RV fractional area change was reduced. Thus, functional evaluation revealed a reduction in systolic deformation of RV basal segments, particularly in the presence of RV dilatation. Interestingly, pulsed-wave Doppler indexes of diastolic function of both the RV and LV were not altered by the number of training hours, and were similar to those of nonathletic subjects. Complex ventricular arrhythmias can accompany the functional changes in the athlete’s heart, and often they originate from the RV. Angiographic RV ejection fraction was significantly reduced in individuals with ventricular tachycardia, and desmosomal gene mutations were found less commonly than anticipated by the RV cardiomyopathic phenotype. Collectively, these observations indicated that long-term intensive exercise training causes RV changes that are less benign than postulated by some, and that proarrhythmic remodeling of the RV myocardium could account for the ventricular tachycardias in a subpopulation of athletes.

Atrial dimensions were also found to be increased by long-term, intense exercise. In previous studies, atrial fibrillation was higher in sportsmen than in the general population. Increased parasympathetic and decreased sympathetic tone, atrial enlargement, and increased inflammation can all contribute to this higher prevalence. Interestingly, the risk of atrial fibrillation (in men <50 years of age and in joggers) decreased with the aging of this population, and was likely offset by the beneficial effects of vigorous exercise on other proarrhythmic risk factors. Thus, the shape and function of the heart adapt with the intensity and type of the exercise, but with extreme activity, the RV and the atria adapt disproportionately (compared with the LV), potentially generating a substrate for arrhythmias. Unfortunately, there is very little information about myocardial tissue alterations that form the substrate for arrhythmias.
in the athlete’s heart, for obvious reasons. In autopsy-based surveys of populations of young athletes in the United States, hypertrophic cardiomyopathy was the most common (26.4%) cause of sudden death.12 Myocyte disarray, electric remodeling, and replacement fibrosis likely contributed to the occurrence of lethal reentrant ventricular tachycardia in these cases. Besides other known cardiovascular pathological diagnoses, like arrhythmogenic RV cardiomyopathy, LV hypertrophy of undetermined cause was found in a significant minority of the fatalities (7.5%).12 A recent case report details the postmortem findings of a highly trained marathoner who died suddenly while running.13 The authors argued that significant LV hypertrophy and interstitial myocardial fibrosis throughout both chambers could be the result of long-term repeated strenuous exercise by the unfortunate runner, whereas other causes were considered less likely.13 An association of these tissue changes and lethal arrhythmia was implied. In one preliminary magnetic resonance imaging study, evidence for the increased incidence of myocardial fibrosis in elite high-endurance athletes was associated with depressed cardiac function.14 If confirmed in large series, this could have great implications for magnetic resonance imaging in the preparticipation screening and diagnostic follow-up of athletes.

In this issue of Circulation, Benito et al15 present very interesting data on cardiac fibrosis, venricular function, and arrhythmia inducibility in a rat model of long-term endurance exercise training. Pathogen-free, 4-week-old male Wistar rats were subjected to a progressive training program of running on a treadmill, initially at a slow pace for short periods, but gradually building up to steady-state running at 60 cm/s for 60 minutes (ie, 2.16 km/h = 1.34 miles/h). Animals were included in this study only if they ran at this level 5 d/wk for 4, 8, or 16 weeks. The investigators estimated how this rat exercise program would compare with human activity, and proposed it to be equivalent to ≈10 years of daily training in humans at ≈90% of predicted maximum heart rate,15 not unlike the exercise performance of long-distance runners. Hence, for the animal model used in this study, the name “marathon rat” is appropriate.

The investigations by Benito et al are original for several reasons: (1) Temporal patterns of collagen deposition and molecular fibrosis markers were characterized in all 4 cardiac chambers until 16 weeks of daily exercise; (2) arrhythmia inducibility was tested at 16 weeks with RV electric stimulation; and (3) the reversal of cardiac remodeling was examined after exercise cessation.

Marathon rats exhibited cardiac adaptations that were also found in human athletes, including LV (but not RV) wall thickening, along with mass increase, indicating hypertrophy. Serial echocardiograms revealed LV dilatation at 16 weeks, biventricular diastolic dysfunction at 8 to 16 weeks, and left atrial enlargement. Of note, the RV was not significantly dilated compared with sedentary control rats, which is at variance with extreme human exercise. Histological and biochemical markers of tissue fibrosis were increased in the RV, but not in the LV or interventricular septum. In addition, whereas mRNA and protein expressions of transforming growth factor-β1 (TGF-β1), fibronectin-1, matrix metalloproteinase-2, tissue inhibitor of metalloproteinases 1, procollagen-I, and procollagen-III were differentially increased in the RV and atria at 16 weeks, no such changes were observed in the LV. From these results, the explanation for diastolic dysfunction appears discrepant for the LV versus the RV.

Different, but overlapping, axes of cellular signal transduction produce physiological versus pathological hypertrophic remodeling,16 and their activation is determined, at least partly, by the intensity and duration of cardiac (over)load. Central to the profibrotic response under pathological conditions is the renin-angiotensin-aldosterone system. Local angiotensin II activates fibroblasts to produce collagen and other extracellular matrix proteins, but also acts via autocrine mechanisms through TGF-β1. Paracrine activation of myocytes by angiotensin II induces p38 mitogen–activated protein kinase to stimulate collagen production, which is also implied. Moderate exercise training and losartan treatment proved beneficial in a rat model of myocardial infarction by attenuating cardiac fibrosis and preserving postinfarct function.17

There was no mention of sudden death, spontaneous ventricular tachycardia, or atrial fibrillation in the marathon rats, which were not telemeterized.19 Slight ventricular conduction delay was noted at 16 weeks, as manifested by a 1.7 ms increase in the QRS duration. Programmed electric stimulation from the RV apex led to sustained ventricular tachycardia more often in exercised rats than in sedentary controls. It is tempting to speculate about a role for cardiac fibrosis in QRS widening and arrhythmia susceptibility, as the authors do, but other factors should also be taken into account. Wiegerinck et al18 indicated that increased myocyte size during hypertrophy, together with decreased longitudinal conduction velocity (by reduced connexin 43 expression), led to prolonged QRS duration even in the absence of altered fibrosis. In addition, despite the absence of changes in the RV effective refractory period, a potential proarrhythmic contribution of altered repolarization characteristics cannot be readily dismissed on the basis of the present data. Ion currents were not investigated. In a previous study on female rats subjected to 6 weeks of wheel running exercise, LV epicardial myocytes showed decreased transient outward K+ current, along with significant monophasic action potential prolongation.19

Electrophysiological follow-up during detraining was not included in the present study. What would happen with the induction of arrhythmia after cessation of exercise at a stage (8 weeks) when structural remodeling, fibrosis, and profibrotic molecular markers have almost completely regressed to control levels? The answer to this question is extremely relevant, given scattered information in the literature that...
electric remodeling under various pathological conditions cannot (easily) be reversed, and given clinical observations that the frequency and complexity of ventricular arrhythmias decrease in the majority of trained athletes after detraining.20

In closing, the balanced cardiac adaptations to moderate exercise are an act of physiology, and it should be emphasized heavily that a sportive lifestyle brings many physical and mental benefits. In addition, exercise is a powerful tool in the treatment of patients with heart failure. However, concerns remain with regard to the cardiac consequences of extreme exercise in fanatic athletes. The elegant results of Benito et al15 fuel the debate on this topic but await confirmation in humans. Modern imaging techniques and tissue characterization will answer critical questions about the athlete’s heart.

An old adage prevails: “Too much of anything is good for nothing.”

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None.

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