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EDITORIAL COMMENT

Focal Fibrosis in the Endurance Athlete's Heart

Running Scarred or Running Scared?*

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It's a shallow life that doesn't give a person a few scars

—Garrison Keillor (1)

The heart of the athlete is strong; the life of the athlete is long. With rare exceptions, these statements are incontrovertible facts supported by a wealth of data. Exercise-induced cardiovascular remodeling, the process that defines the endurance athlete's heart, is characterized by biventricular dilation with supranormal diastolic function, biatrial dilation, and enhanced arterial vasomotor function (2). These adaptive attributes facilitate maintenance of high cardiac output during endurance exercise and may deter age-related adverse cardiac deconditioning (3). In addition, mortality data suggest that endurance athletes, even those who competed only early in life, live longer than their nonathletic counterparts (4) and tend to use fewer health care resources (5). Nonetheless, long-term commitment to competitive athletics or a highly active lifestyle does not confer complete immunity from cardiovascular disease. Aging endurance athletes often develop acquired cardiovascular conditions including atherosclerotic heart disease, atrial arrhythmias, and hypertension, and it has recently been suggested that sport itself may play a role in disease pathogenesis. This hypothesis, as it relates to atrial tachyarrhythmias and coronary artery calcification, is under active investigation. Should we add heart muscle fibrosis to the list of potential overuse pathologies?

In this issue of *iJACC*, Tahir et al. (6) present data examining the prevalence of myocardial fibrosis, as delineated by late gadolinium-enhancement (LGE) cardiac magnetic resonance (CMR) and its relationship with cardiopulmonary exercise testing data and lifetime exercise exposure among middle-aged triathletes (6). The authors studied 83 asymptomatic athletes (43 ± 10 years of age; 65% male) and 36 normally active (1.3 ± 0.8 h of weekly exercise) controls by using CMR and bicycle ergometer cardiopulmonary exercise testing. Indicating successful recruitment of accomplished athletes, triathletes demonstrated superior exercise capacity as assessed by peak oxygen consumption, larger left ventricular mass, and larger biventricular chamber volumes than control participants. Most notably, CMR demonstrated small amounts of focal "nonischemic" LGE (3.5 ± 2.8% of total left ventricular [LV] myocardium) in 9 of 83 triathletes (11%), all of whom were men. Careful inspection of representative CMRs revealed important heterogeneity with subepicardial localization, consistent with possible prior myocarditis in 5 of 9 athletes; isolated right ventricular (RV) insertion point LGE, a pattern associated with RV pressure overload in 2 of 9 athletes; and nonspecific subendocardial myocardial fibrosis revealed by LGE in the remaining 2 men. Compared to athletes without scarring, triathletes in whom myocardial fibrosis was detected by LGE (LGE^+) had higher LV mass, which was accounted for by expansion of the extracellular compartment, a trend toward higher resting systolic blood pressure, and higher peak exercise blood pressure (213 ± 24 vs. 194 ± 26 mm Hg, respectively; $p < 0.05$). In addition, LGE^+ triathletes reported swimming and cycling farther distances and participating more frequently in longer distance triathlon races than their counterparts in whom myocardial fibrosis was not detected by LGE (LGE^-) during the 3-year period prior to study enrollment. Multivariate analysis identified peak exercise systolic blood pressure and aggregate competition swimming as independent predictors of LGE^+.

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The story of myocardial fibrosis among competitive athletes began roughly a decade ago and continues to unfold. In 2009, Breuckmann et al. (7) reported on 102 "ostensibly healthy" male marathon runners who demonstrated an LGE^+ prevalence of 12%, compared to 4% in their control population ($p = 0.07$); fibrosis was anatomically distributed into 2 categories: a coronary artery disease pattern and a noncoronary pattern. That paper was followed by tandem reports of myocardial fibrosis among lifelong, veteran endurance athletes ($n = 12$; 56 ± 6 years of age; 50% LGE^+) (8) and younger competitive endurance athletes ($n = 39$; 37 ± 8 years of age; 15% LGE^+) (9). The latter paper, elegantly presented by La Gerche et al. (8), included physiological data surrounding long-duration endurance races and demonstrated transient RV dilation and dysfunction, a process proposed as the key step in the causal pathophysiological myocardial fibrosis pathway. Since these sentinel papers, additional observational series with mixed findings, including some athlete cohorts totally devoid of myocardial fibrosis (10,11), have been published. Data now presented by Tahir et al. (6) further advance our understanding of cardiac fibrosis in athletes in 2 meaningful ways. First, their study confirms that a minority of healthy athletic men (i.e., asymptomatic and athletically capable) may demonstrate LGE^+ during CMR interrogation. Second, their study provides some speculative insights into the pathophysiology of this process by suggesting a role for exercise-induced systolic hypertension, a hemodynamic mechanism, and cumulative exercise exposure, an exercise dose-dependent mechanism. However, scientists and clinicians are still left with more questions than answers. Cardiac fibrosis has been observed among the fittest and most physically capable segment of the human population. Why does this happen and, perhaps more importantly, why should we care?

LGE CMR is thought to reflect scar tissue, the permanent byproduct of a heart muscle injury severe enough to trigger necrosis and replacement fibrosis. Among athletes, there are numerous reasons why fibrosis might occur. Aging athletes are susceptible to atherosclerotic coronary disease, and attendant myocardial infarction is an important cause of scar in this population. Beyond ischemia, the list of potential causes mirrors the differential diagnosis among non-athletes with several nuanced caveats. Subclinical myocarditis, a disease with an unknown incidence, is likely the most important cause of patchy, diffuse free-LV wall fibrosis in athletes. The combination of subclinical infection coupled with continuation of high-intensity/high-volume exercise, a combination shown to be deleterious in animal models (12), likely explains a significant percentage of the nonischemic fibrosis seen in athletes. Importantly, the myocarditis-fibrosis paradigm represents a "two-hit process" in which the combination of an injury, inflammation, and cellular dysfunction induced by infection is exacerbated to the point of permanent damage by the superimposition of the hemodynamic stress of endurance exercise. The concept that it takes more than high doses of exercise in isolation is substantiated by the fact that, to date, every athlete CMR series shows that afflicted individuals represent the exception rather than the norm. Additional injurious process including the myocardial toxicity of illicit performance-enhancing drugs, excessive hemodynamic pressure, and/or volume overload due to abnormal systemic and/or pulmonary vasomotor function, and perhaps unidentified genetic predispositions, likely behave in similar fashions when superimposed on intense exercise. Future work focusing on cause and mechanism is required to clarify this cardinal area of scientific uncertainty.

More important than understanding why scarring develops is determining its clinical relevance. Among symptomatic athletes presenting with high-risk features including malignant arrhythmias or ventricular systolic dysfunction, scars may be part of the causal pathway and may impart both an increased risk of adverse outcomes during exercise and a low likelihood of spontaneous recovery. Such patients are most effectively managed by an individualized often restrictive exercise recommendations coupled with medical and device/catheter directed therapy. Unfortunately, we know comparatively less about the population of men, asymptomatic and normally performing competitive athlete, studied by Tahir et al. (6) and others. Although it is possible that such athletes represent the proverbial sudden cardiac death canary in the coalmine, it is far more likely that most cases of incidentally detected scarring represent benign evidence of prior cardiac injury. CMR is a powerful tool and represents a key step in the assessment of athletes with suspected myocardial disease. As its use continues to increase, we will be increasingly faced with incidentally detected nonischemic fibrosis. Patients who harbor this finding want to know what it means and what to do about it. At present, these are unanswerable questions. Until we learn more, our approach to such patients should include shared decision making with transparent

acknowledgment of uncertainty, a thoughtful diagnostic approach to nonischemic causes of heart muscle injury, and measured risk stratification using maximal effort limited exercise testing and comprehensive ambulatory rhythm monitoring. There is indeed more work to be done to clarify the pathogenesis and clinical relevance of focal nonischemic scar tissue in the heart of the athlete. Although we await more data, it seems prudent to treat the patient, not the images, as over-reacting to incidental scar may have the potential to do more harm than good.

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