

## Endurance Exercise and the Right Ventricle Weak Link, Innocent Bystander, or Key Ingredient?

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The cardiovascular response to high-intensity exercise has intrigued clinicians and scientists for more than a century. Since the initial reports of cardiac enlargement among Nordic skiers<sup>1</sup> and rowers,<sup>2</sup> a great deal has been learned about how the heart and vasculature remodel in response to endurance exercise. Through the efforts of many investigators and their athletic subjects, we now recognize the heart as an organ characterized by tremendous plasticity that permits chamber dilation and myocardial hypertrophy in response to the hemodynamic stressors inherent in endurance sporting activity. Our contemporary view of the endurance athlete's heart includes attributes such as biventricular and biatrial dilation, mild to moderate ventricular hypertrophy, and normal to mildly reduced resting biventricular systolic function (as defined by ejection fractions).<sup>3</sup> Functionally, this remodeling pattern facilitates stroke volume augmentation and thus increases cardiac output reserve during exercise. Yet, are these adaptations that facilitate successful endurance sport participation and lead to optimal athletic performance cost free? More specifically, do the short-term physiological benefits of exercise-induced cardiac remodeling come with long-term trade-offs that have undesirable clinical consequences?

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These are not new questions. For as long as exercise-induced cardiac remodeling has been recognized, its clinical relevance with respect to health and longevity been questioned. In his sentinel 1899 article describing physiological adaptations in Harvard oarsmen, Thomas Darling wrote: "We have seen that a great increase in size and strength is demanded of this organ (the heart) and it may easily happen that it is called on for more work than it is able to do and that instead of establishing a compensatory hypertrophy it becomes diluted and weakened. A 'broken-winded' athlete is probably one with a dilated, flabby heart."<sup>2</sup> The principal question raised by Darling and many of his successors – Can the adaptive response to endurance exercise transition into pathology with relevance to both performance and health? – remains a topic

plagued by considerable uncertainty and thus fertile grounds for active debate.<sup>4,5</sup>

Recently, the right ventricle (RV) has assumed a prominent place in this dialogue. Under resting conditions, the RV does less work than the left ventricle (LV) to generate matched stroke volumes because of the relatively low afterload imparted by the pulmonary vasculature. Yet during exercise, RV afterload may increase disproportionately to LV afterload, thereby translating into a higher relative change in RV wall stress in comparison with the LV. In addition, the RV and the interventricular septum, a structure formed by interdigitation of myocardial fibers from both the LV and RV, appears to be particularly susceptible to fatigue following isolated endurance events<sup>6</sup> and sustained periods of training.<sup>7</sup> It is now firmly established that the RV is often markedly dilated among endurance athletes,<sup>8,9</sup> and it has been reported that athletes presenting with symptomatic ventricular arrhythmias commonly demonstrate RV foci.<sup>10</sup> Proarrhythmic patches of fibrosis within the RV and interventricular septum, hypothetically caused by repeated bouts of endurance exercise-induced injury and repair, have been proposed as a unifying pathogenic mechanism. Yet to be certain, data defining the scope of this problem and a causal relationship between intensive endurance exercise, cardiac scarring, and clinically relevant arrhythmias are lacking. This plausible yet unsubstantiated hypothesis remains to be rigorously tested.

In this issue of *Circulation*, Bohm and colleagues<sup>11</sup> report timely data that advance this discussion. This German investigative team hypothesized that veteran elite-level endurance athletes would demonstrate evidence of RV injury as defined by disproportionate chamber dilation, impaired systolic function, or myocardial scarring. To test this hypothesis, the authors recruited and studied 33 healthy, white male endurance athletes (age range, 30–60) and a sex-matched sedentary comparator group. The athletes were required to have accumulated at least 10 years of training during which training volume (ie, exercise dose) was at least 10 hours per week. Notably, enrollment criteria also stipulated that participants were still engaged in competitive training and racing at the time of study, thus maximizing the opportunity to study overtly healthy competitors. The final athlete selected contained a substantial number of truly elite-level competitors as reflected by professional status, race accomplishments, and laboratory-based physiology testing. Athletes and controls were studied by maximal effort limited cardiopulmonary exercise testing, transthoracic echocardiography, cardiac magnetic resonance imaging, and limited cardiac biomarker profiling. Key findings from this multimodality, cross-sectional phenotyping approach are summarized as follows. First, athletes demonstrated clear evidence of structural exercise-induced

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cardiac remodeling as reflected by relative biventricular dilation and hypertrophy in comparison with controls. Notably, athletes were found to have RV chamber size predominance (as reflected by an LV-to-RV end-diastolic volume ratio <1), a pattern not found in controls. Second, athletes and controls were found to have normal and largely similar resting systolic and diastolic functional parameters of both the right and left ventricles. This observation supports the concept that resting cardiac function in healthy athletes is most commonly within normal limits but at times lies in the low normal to mildly abnormal range. We and others have reported this phenomenon,<sup>12</sup> and a role for exercise provocation coupled with cardiac imaging to document intact contractile reserve has been proposed to address clinical concerns about mildly reduced ventricular function.<sup>13</sup> Finally, only 1 of 33 athletes demonstrated evidence of intramyocardial fibrosis by cardiac magnetic resonance. In the single athlete found to have scarring, the region of fibrosis was limited to the posteroinferior epicardium, a finding the authors attribute to a previous episode of pericarditis. Thus, healthy myocardium with no evidence of fibrosis was the consistent pattern in this group of accomplished and experienced endurance competitors.

The data summarized above provide important pieces to the evolving high-dose exercise puzzle. The finding of disproportionate RV dilation, both with respect to the amount of RV muscle mass and in comparison with the adjacent LV chamber size, provides further data to substantiate the claim that the RV is the most structurally responsive cardiac chamber to endurance exercise training and competition. We are again reminded that the clinical use of RV size cut points to differentiate physiological dilation from important disease processes, including arrhythmogenic RV cardiomyopathy, is of limited value. When faced with an athletic patient with RV enlargement, accurate differentiation of health from disease requires careful examination of non-size-based structural and functional cardiac parameters (sacculations, aneurysmal RV free wall outpouching, segmental dysfunction) coupled with additional clinical data as recently proposed.<sup>14</sup> To what degree disproportionate RV dilation represents injury rather than adaptation remains speculative, but in the absence of concomitant scarring or functional impairment seems an unlikely interpretation.

With respect to the relationship between intensive endurance exercise and cardiac damage, the present study provides an important complement to data presented by La Gerche et al<sup>15</sup> several years ago. In this previous study, 5 of 40 (12.8%) experienced, middle-aged ( $37\pm 8$  years of age) endurance athletes were found to have cardiac magnetic resonance evidence of myocardial fibrosis, and athletes with scarring demonstrated significantly larger RVs with lower indices of RV systolic function in comparison with athletes without scarring. It has since been suggested that cardiac scarring in endurance athletes results from repetitive myocardial injury caused by long-term exposure to endurance exercise. Now, Bohm et al present a similar cohort with no evidence of myocardial scarring. What explains the fact that these 2 relatively similar cohorts with respect to recruitment strategy, baseline characteristics, and investigative protocol could yield such different results? As is often the case, careful consideration of study designs holds several potential answers.

The authors of both studies are to be commended for responsibly studying an intriguing topic and, in both cases, for being forthcoming with the limitations of their work. In addition, such studies are limited in their ability to capture the full-breadth phenotypic diversity and are not capable of establishing cause-and-effect relationships. Close examination of the structural and functional cardiac parameters presented in both studies shows that elite-level endurance athletes, like most other populations, demonstrate significant heterogeneity and follow their own normal distributions. Bohm et al nicely address this topic through their discussion of RV ejection fraction, which displayed a wide range of values in their cohort. At the present time, we understand very little about why such variability exists. It is possible, if not probable, that athletes not only demonstrate variability in resting cardiac measurements, but also respond in a heterogeneous fashion, both with respect to health and performance, to chronic endurance exercise training. The chronic high-dose exercise stimulus that leads to marked but healthy adaptation in 1 athlete may, for a myriad of reasons, lead to injury in another.

Finally, we are left to consider the issue of causality. Both studies discussed above contain relatively small, cross-sectional data sets that are inherently prone to both type 1 and 2 errors. Thus, to conclude that fibrosis either is or is not caused by sport is premature and worthy of future investigation. If one takes the liberty of pooling the available data, we are left with 73 elite competitors, in which only 6 demonstrated some detectable form of focal fibrosis. It is possible that these 6 athletes were outliers with respect to exercise dose exposure (the combination of intensity, duration, and frequency) and that indeed the observed fibrosis represents an overexposure toxicity phenomenon. Yet, the available data provide no compelling reason to accept the simplistic interpretation. More likely, cardiac fibrosis among veteran endurance athletes represents a more complex, multihit process. As recently suggested,<sup>16</sup> it is probable that both high-dose endurance exercise training and either some critical yet still unidentified host factor or concomitant exposure to a more definitively injurious process (ie, occult myocarditis, surreptitious illicit performance enhancing drug use) are required to produce cardiac scarring.

In summary, this study by Bohm et al provides welcomed normative cardiac remodeling data in veteran elite endurance athletes. The finding of marked RV remodeling in the absence of overt dysfunction or scarring is reassuring and challenges the notion that high-dose exercise injures the heart. However, a challenged notion is not a definitive answer. A comprehensive understanding of how high-dose exercise impacts health and longevity will require future long-term, longitudinal studies using precision phenotyping of ethnically diverse athletes representing numerous endurance sporting disciplines. In the absence of definitive data, clinicians charged with the care of athletic patients may be most effective when they acknowledge uncertainty and rely on practicality. In the time-honored 1899 words of Thomas Darling, athletes seeking the optimal balance of performance and health should be counseled to “not throw too much work on the muscles and especially on the heart until they are strengthened by preliminary work, to watch nutrition carefully, and to avoid nervous fatigue by

providing a certain variety of exercise and by not confining the attention too closely to the approaching contest.”

### Disclosures

None.

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