# Coronary Artery Calcification Among Endurance Athletes

## "Hearts of Stone"

Articles, see p 126 and p 138

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*…cause you'll never break, never break, never break, this heart of stone.*
—Mick Jagger and Keith Richards, The Rolling Stones, *Heart of Stone*, 1964

Routine moderate-intensity exercise reduces incident cardiovascular disease and increases longevity. The complex mechanisms by which exercise promotes favorable cardiovascular health outcomes include attenuation of traditional atherosclerotic risk factors including dyslipidemia, hypertension, central adiposity, and glucose intolerance. As such, current physical activity guidelines recommend either 150 minutes of moderate-intensity exercise or 75 minutes of higher-intensity exercise weekly.[1] This recommendation is justified by a broad epidemiological and exercise intervention literature base and represents the current standard of cardiovascular care for all patients.[2]

However, the dose-response relationship between exercise and health outcomes, in particular, at exercise doses that exceed current recommendations, remains incompletely understood. For example, highly fit individuals have reduced risk of sudden cardiac death[3] and development of heart failure,[4] with little evidence of a plateau at high levels of fitness.[5] Competitive athletes, people who in engage in very high levels of exercise over many years and in some cases a lifetime, typically live longer than sedentary and normally active people,[6] and develop beneficial adaptive cardiovascular traits including physiological myocardial remodeling[7,8] and increased myocardial[9,10] and vascular compliance. Conversely, athletes and highly active people are not immune to cardiovascular disease. Sudden cardiac death certainly occurs among this population, and atherosclerotic coronary disease is the most common etiology of death during sport among those >35 years of age.[11,12] Recent data have unexpectedly raised the possibility that long-term, high-volume endurance exercise may actually accelerate rather than reduce coronary atherosclerosis.[13] This controversial hypothesis has been passionately debated and remains a key issue of uncertainty in the clinical care of athletic patients.

In this issue of *Circulation*, 2 studies present data examining coronary artery morphology among middle-aged endurance athletes.[14,15] Merghani et al[15] recruited 152 competitive cyclists and runners (age=55±9 years) and a normally active, age-matched control cohort without a previous diagnosis of coronary artery disease, a family history of premature coronary artery disease (<40 years), diabetes mellitus, hypertension, hypercholesterolemia, and active or prior tobacco smoking. Coronary computerized tomography angiography revealed that the majority of athletes (60%) and control participants (63%) had no demonstrable coronary artery calcification (CAC). However, male athletes had a higher prevalence of atherosclerotic plaque with luminal irregularity (44% versus 22% in controls) with plaques composed predominantly of calcium. Among athletes, a CAC score

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>70th percentile was modestly but significantly associated with number of years of exercise training. The authors conclude that, although the majority of aging endurance athletes demonstrates no appreciable CAC, athletic men are more likely than normally active men to have calcific coronary plaques despite the absence of potentially explanatory traditional cardiovascular risk factors. In the second study, Aengevaeren and colleagues[14] report similarly obtained coronary computerized tomography data on men >45 years of age who participated in in the MARC study (Measuring Athletes Risk of Cardiovascular Events). This Dutch cohort comprised men (55±7 years of age) without previously diagnosed coronary disease who sought medical evaluation for cardiovascular risk assessment or exercise testing to determine performance metrics. Each participant's lifelong exercise history was assessed by retrospective recall, and participants were stratified into 3 broad categories: <1000, 1000 to 2000, and >2000 estimated metabolic equivalent of task-minutes per week. Coronary computerized tomography angiography revealed CAC in approximately half of the participants (53%) with athletes in the highest exercise dose category demonstrating significantly higher CAC scores and calcific plaque burden than participants with less exercise exposure. When only the individuals with measureable CAC were considered, however, there was no effect of increasing exercise dose. The authors conclude that high-dose exercise is associated with a higher prevalence of CAC and atherosclerotic plaque with a tendency for plaque to be calcified rather than mixed, and therefore more benign. In aggregate, data from these studies suggest that a significant minority of long-term endurance athletes will develop CAC and predominantly calcific plaques that cannot be explained by typical mediators of coronary artery disease.

Data derived from these studies represent important contributions to the sports cardiology literature but raise as many questions as they answer. The residual areas of scientific and clinical uncertainty regarding CAC in aging endurance athletes may best be addressed by consideration of the inherent limitations of these studies with an emphasis on 3 issues: (1) limitations of cross-sectional data, (2) potential influence of unmeasured confounders, and (3) absence of clinical outcomes. The cross-sectional study design, used both in these 2 new studies and in the prior study of German marathon runners,[13] is well suited for documenting associations but is not capable of establishing cause-and-effect relationships between exposures and clinical phenotypes. Although it is reasonable to conclude that aging endurance athletes may harbor significant, perhaps unexpectedly high amounts of CAC, underlying mechanisms remain speculative. Although tempting, it remains premature to conclude that high doses of exercise play a primary mechanistic role in the development of CAC.

Although it is possible that the hemodynamic and mechanical factors inherent in endurance exercise may lead to arterial wall injury and recovery calcification, this hypothesis remains speculative. If it were this simple, one would expect CAC to be present in all or at least the vast majority of endurance athlete participants in both studies. Because this was not the case, we are left to consider what factors differentiate those athletes that calcify from those that do not. Although both studies attempted to adjust for traditional atherosclerotic risk factors, additional potential explanatory factors such as dietary intake, psychological stress, chronic inflammation/anti-inflammatory medication use, and underlying atherosclerotic genetics were not sufficiently adjusted for. For example, many endurance athletes engage in relatively unhealthy, proatherogenic dietary patterns that go underappreciated in both clinical and research settings because of the athlete's ability to maintain lean body profiles attributable to high caloric expenditure. In addition, both studies appear to be susceptible to recruiting preferentially those athletes who might be particularly worried about their cardiovascular health and therefore are prone to selection bias. Without adjusting for these confounders, it remains uncertain why some aging endurance athletes harbor high levels of CAC.

Finally, and perhaps most importantly, it is important to acknowledge the complete absence of clinical outcomes data in athletes with CAC. Although CAC in sedentary and/or normally active cohorts has been associated with adverse cardiovascular outcomes, no similar data are available for highly active individuals. We urge caution against the reflex generalization of data derived from nonathletic populations in this setting, and longitudinal studies powered to define the prognostic significance of CAC among aging athletes are warranted. Although it is possible that CAC among endurance athletes may carry similar negative prognostic implications to those established in other populations, this may not be the case. It is possible that the presence of CAC among dedicated lifelong endurance athletes may very well represent a clinically benign phenotype.

At present, the optimal role of noninvasive coronary artery morphology assessment and the clinical application of data derived from such testing among athletic patients remains uncertain. Future work will be required to determine the mechanisms and prognostic significance of CAC in aging endurance athletes. Understanding the nuances of plaque composition, total plaque volume and distribution, and their relationship with exercise dose (duration, frequency, intensity), and traditional and emerging atherosclerotic risk factors, as well, will be critical. While we await further data, we offer several considerations that emerge from our work as directors of high-volume sports cardiology programs. First, the mainstay of optimal athletic patient management does not require CAC data but

rather a reliance on conventional risk factors including lipid profiles, ambulatory blood pressure monitoring, and functional exercise testing designed to simulate the physiological demands of training and competition. Second, in limited situations, CAC data may provide adjunctive information for patients who resist medical therapy for established risk factors (ie, statins and antihypertensive therapy). However, the growing availability of and enthusiasm for CAC scoring has led to increases in the number of aging athletes with apparent subclinical disease. When presented with such athletes, we currently do not recommend reductions in exercise exposure but rather rely on strategies targeting the modification of traditional and emerging atherosclerotic risk factors, and, of course, prudent shared decision-making discussions with the patient about individual goals of training and competition. We have much to learn about coronary artery physiology among people that push the body to its limits and beyond. But, as we continue this journey and diagnostic technology advances in parallel, it remains prudent to minimize the application of testing with uncertain relevance.

## DISCLOSURES

None.

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## FOOTNOTES

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