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Review Article

Coronary artery calcification in endurance athletes: a narrative review

Calcificação na artéria coronária em atletas de endurance: uma revisão narrativa

Gabriele Justo Canevazzi[1], Francielle Santos Almeida[1], Adriana Boiteux do Carmo[2], Marianne Peixoto Sobral Giroldo Badessa[3], Pedro Gabriel Senger Braga[4], Marcelo Luiz Peixoto Sobral[5]

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ABSTRACT: Introduction: cardiovascular disease is the leading cause of death worldwide and coronary artery disease stands out for the number of deaths. Increased coronary artery calcification is a risk factor for coronary events. However, healthy adult men with a high lifelong exercise volume and with a history of endurance training demonstrate high CAC values. Objective: Considering the apparent paradox between the effects of strenuous physical training and the development of CAC, the present study aims to evaluate the mechanisms of CAC in physically active adult men. Methods: This study is a narrative review of scientific productions in Portuguese and in English found in the following databases: National Library of Medicine (PubMed), Scientific Electronic Library Online (SciELO) and US National Library of Medicine (NLM). Results: In a study, 150 of 284 participants (53%) had a median CAC score of 35.8 [9.3-145.8]. The average lifetime exercise volume was 2.9 [1.9-4.4] hours/week, resulting in 1356 [851-2030] metabolic equivalent of task (MET)-min/week. In addition, CAC was more common in athletes with higher lifelong exercise volumes. As in other studies, higher CAC scores and greater coronary plaques in athletes can be interpreted as a deleterious effect of exercise on the coronary arteries. However, the calcific and stable nature of the plaques in male athletes can also be considered as protective against plaque rupture and acute myocardial infarction. Conclusion: Endurance athletes are more predisposed to increased coronary artery calcification than less active or sedentary individuals. However, it is observed is that higher lifelong exercise volumes seem to be associated with more benefits than cardiovascular risks.

Keywords: Vascular calcification; Athletes; Cardiovascular diseases.

RESUMO: Introdução: a doença cardiovascular é a principal causa de morte em todo o mundo e a doença arterial coronariana se destaca pelo número de óbitos. A calcificação da artéria coronária (CAC) aumentada é um fator de risco para eventos coronarianos, no entanto, homens adultos saudáveis com alta carga de treino ao longo dos anos e com histórico de longas provas de resistência demonstram altos valores de CAC. Objetivo: tendo em vista o paradoxo existente entre os efeitos do treinamento físico extenuante e o desenvolvimento da calcificação coronariana, o presente estudo tem como objetivo avaliar o mecanismo da CAC em homens adultos fisicamente ativos. Métodos: Este estudo caracteriza-se como uma revisão narrativa, tendo como base, produções científicas nas línguas portuguesa e inglesa, nas seguintes bases de dados: National Library of Medicine (PubMed), Scientific Eletronic Library On-line (SciELO) e US National Library of Medicine (NCBI). Resultados: Em um estudo, 150, dos 284 participantes (53%), tinham o escore de CAC mediano de 35,8 [9,3-145,8]. O volume médio de exercício ao longo da vida foi de 2,9 [1,9-4,4] horas/semana, resultando em 1356 [851-2030] equivalentes metabólicos de tarefa (MET)-min/semana. Além disso, a presença da CAC foi mais comum naqueles com maiores volumes de exercícios ao longo da vida. Assim como em outros

1. Graduada em Medicina pelo Centro Universitário das Américas (FAM), São Paulo, SP. ORCID: Canevazzi GJ - https://orcid.org/0000-0002-1351-5033; Almeida FS - https://orcid.org/0000-0003-0041-3705. E-mail: gabrielecanevazzi@gmail.com, franmed.sa@gmail.com.
2. Graduanda em Medicina, Centro Universitário das Américas (FAM). São Paulo, SP. https://orcid.org/0000-0003-2185-3224. E-mail: adrianaboiteux-docarmo@gmail.com.
3. Mestre pela UNIFESP e docente no curso de medicina do Centro Universitário São Camilo, São Paulo, SP. https://orcid.org/0000-0002-7855-1799. E-mail: mariannesobral@hotmail.com.
4. Laboratório de Metabolismo de Lípides do Instituto do Coração (InCor), Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo (HC-FMUSP). São Paulo, SP. https://orcid.org/0000-0002-6690-6345. Email: Pedro.senger@gmail.com.
5. Doutor em ciências pela Universidade de São Paulo (USP), Departamento de Cirurgia Cardiovascular e Torácica, Instituto do Coração, São Paulo, SP. Docente no curso de medicina do Centro Universitário das Américas (FAM) e do Centro Universitário São Camilo, São Paulo, SP. https://orcid.org/0000-0003-3431-7033. E-mail: marcelo.sobral@fm.usp.br.

Endereço para correspondência: Rua Bela Cintra, 672 apt 910. Consolação - São Paulo, SP, Brasil. CEP: 01415-000

trabalhos, pode-se considerar que maiores pontuações da CAC e maiores placas coronárias em atletas podem ser interpretados como um efeito deletério do exercício nas artérias coronárias, entretanto, a natureza calcificada e estável das placas em homens atletas também podem ser considerada como protetora contra a ruptura da placa e infarto agudo do miocárdio. Conclusão: Os atletas de endurance estão mais predispostos ao aumento da calcificação da artéria coronária que indivíduos menos ativos ou sedentários, contudo o que se observa é que as altas cargas de exercício físico ao longo da vida parecem promover mais benefícios do que risco a saúde cardiovascular.

Palavras-chave: Calcificação vascular; Atletas; Doenças cardiovasculares.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of death in the world, and coronary artery disease (CAD) caused by atherosclerosis is responsible for the highest number of deaths, especially among men[1]. Atherosclerosis is associated with an accumulation of oxidized lipids and fibrotic material and an increase in inflammatory cytokines. It is a slow process that takes years to manifest. As the disease progresses, arteries become blocked, reducing the local blood flow and the supply of oxygen and nutrients to the tissues, leading to ischemia. CAD manifests as angina and infarction, predominantly after the fifth decade of life[2].

On the other hand, physical activity and physical training can reduce CVD morbidity and mortality. The benefits of physical activity to cardiovascular health can already be observed with only 15 minutes of physical activity per day, which is associated with a 14% reduction in mortality[3]. However, some studies have reported that excessive physical training could have deleterious effects on cardiac function, including coronary artery calcification (CAC)[4-6]. CAC is an important risk factor for coronary events in asymptomatic individuals, especially those with CAC $\geq$ 100 Agatston units. Even though physical activity has been associated with increased longevity and remarkable reductions in cardiovascular events and mortality[7], studies have shown that ultradistance and marathon runners have higher CAC scores when compared to runners participating in shorter events[8].

OBJECTIVE

Considering the apparent paradox between the effects of strenuous physical training and the development of CAC, the present study aims to evaluate the mechanisms of CAC in endurance athletes.

METHODS

This study is a narrative review of scientific productions preferably from 2010-2020, in Portuguese and in English, found in the following databases: National Library of Medicine (PubMed), Scientific Electronic Library On-line (SciELO) and US National Library of Medicine (NLM). The descriptors used were "coronary artery calcification" and "exercise training" - 315 articles, "coronary artery calcification" and "middle age men" - 1035 articles, "coronary artery calcification" and "marathon" - 14 articles, "coronary artery calcification" and "endurance athlete" - 41 articles. After this survey, the following steps were followed: selective reading and selection of material aligned to the objective of the study; analytical reading and analysis of texts; interpretative reading and writing of the text. Among the publications found, 60 had significant contributions to this study. As this is a narrative review, approval from an Ethics and Research Committee was not required.

RESULTS

In a study by Aengevaren et al.[5], 150 of 284 participants (53%) had a median CAC score of 35.8 [9.3-145.8]. The average lifetime exercise volume was 2.9 [1.9-4.4] hours/week, resulting in 1356 [851-2030] metabolic equivalent of task (MET)-min/week. In addition, CAC was more common in athletes with higher lifelong exercise volumes. Those performing >2000 MET-min/week more frequently had CAC>0 (68%) compared with the <1000 MET-min/week group (43%). CAC scores, area, and the number of regions of interest were significantly higher in the group with a training volume > 2000 MET-min/week compared to the group with <1000 MET-min/week. The multivariable-adjusted analysis demonstrated a significantly higher CAC prevalence in the >2000 MET min/week group versus the <1000 MET-min/week group. In summary, the prevalence of CAC was 68% for those with a MET >2000 min/week, in a sample of 75 individuals. Plaque prevalence (calcified, non-calcified, mixed <130 HU or mixed > 130HU) was significantly higher in the most active group (77%) versus the least active group (56%). However, in participants with coronary atherosclerosis, a lower prevalence of mixed plaques was observed in the most active (48%) versus least active group (69%). Furthermore, it was observed that the most active group more often had only calcified plaques compared with the least active group (ORadjusted = 3.57 (95% CI: 1.28 - 9.97). Therefore, the most active group had a more benign composition of plaques, with fewer mixed plaques and often only calcified plaques. These observations may explain the increased longevity observed in athletes. Despite the presence of more coronary atherosclerosis in the more active participants, these data do not suggest that

there is an increase in mortality in these individuals[5].

In the study by Merghani et al.[4] athletes were defined as people > 40 years, of age, who ran ≥ 16 kilometers per week and have continued to do so for at least 10 years, and competed in at least 10 endurance events, including marathons (42.2 km) and half marathons (21.1 km). In this study, an atherosclerotic plaque was defined as an irregularity causing any degree of luminal stenosis. Significant coronary atherosclerosis was defined as a CAC > 70th percentile and/or presence of plaque associated with > 50% luminal stenosis in a single coronary segment. The CAC evaluation showed that most athletes (52% men) and controls (59% men) had a normal coronary artery calcium score (CAC = 0 Agatston units), and only 25 (16%) athletes and 18 (19.5%) controls had a CAC > 70th percentile. Overall, there were no significant differences between athletes and controls with respect to the proportion with CAC = 0 or CAC > 70th percentile. However, when CAC scores were analyzed with respect to absolute values, athletes had a higher prevalence of moderate to severely elevated coronary CAC scores ≥ 300 Agatston units; 12 (11.3%) male athletes had a CAC score ≥ 300 Agatston units versus none of the sedentary men. The median CAC score in male athletes with a CAC > 1 was higher than in sedentary men with CAC > 1, 86 versus 3. Male athletes had a higher prevalence of coronary plaques compared with sedentary males, 47 (44%) versus 12 (22%). Overall, plaques were observed in 106 athletes and 54 controls. In this sample (n=106), the prevalence of CAC was around 48% among those who ran ≥ 10 miles per week for 10 years and competed in a minimum of 10 endurance events. In addition, the prevalence of plaques was 44%, but, of these, 72% were calcified. This demonstrates higher CAC scores and a greater number of atherosclerotic coronary plaques in these individuals. Thus, higher CAC scores and greater coronary plaques in athletes can be interpreted as a deleterious effect of exercise on the coronary arteries. However, the calcific and stable nature of the plaques in male athletes can also be considered as protective against coronary artery disease, plaque rupture and acute myocardial infarction.

DeFina et al.[9] studied 21,758 healthy American men and divided them according to physical activity levels into <1,500, 1,500 to 2,999, and ≥ 3,000 MET-min/wk. The most active subjects, with more than 3000 MET-minutes/week (equivalent to running approximately 6.5 km/d or 250-300 min/wk), were more likely to have a CAC >100 compared with those with lesser amounts of physical activity. Collectively, these results indicate that athletes are more likely to have high CAC than their sedentary peers. This study demonstrated that, although CAC is associated with increased cardiovascular risk among individuals with CAC < 100, mortality was lower in more active individuals compared to less active individuals (<1500 MET-min/wk). Among individuals with CAC > 100, the risk was not significantly different between groups regarding the volume of physical activity. Therefore, even though the increase in the weekly training load is associated with CAC, it is not a causal factor for higher cardiovascular mortality.

The sample of the study carried out by Jafar et al.[10] included 56 runners who had run competitively for 10 years or more. Runners were divided into 3 categories: Group A comprised runners who had competed in at least 10 ultramarathons (races covering more than 50 km) and/or Ironman competitions in 10 years. Group B included runners who had participated in more than 9 marathons over 10 years. Group C comprised runners who had competed in more than 9 shorter races (defined as races covering less than 13.1 miles) over 10 years. A CAC score > 100 was used to define a group at higher risk of future cardiovascular events. Among runners who participated in extreme distance running (groups A and B), 73.3% of runners had CAC scores greater than 0, whereas only 23.1% of group C runners had CAC scores greater than 0. Furthermore, 70% of athletes in group A+B ranked above the 50th percentile, while only 19.2% of group C runners were ranked above the 50th percentile. About 10% of runners in group A+B had CAC scores > 100, compared with only 11.5% of runners in group C. In summary, ultradistance and marathon runners had higher CAC scores than runners who participated in shorter events[10].

DISCUSSION

Analyzing aspects of the evolution of atherosclerosis is crucial for understanding the outcome of events and even the CAD-related mortality[11]. Different risk factors working together can determine the occurrence of atherosclerosis[12]. These factors can be divided into modifiable (smoking, sedentary lifestyle, obesity, stress, dyslipidemia, and arterial hypertension) and non-modifiable (diabetes mellitus, familial hypertension, thrombophilia, gender, age, and heredity)[13]. Atherosclerosis is an inflammatory and proliferative disease that progresses with the continuity of these mechanisms, or abruptly, with thrombotic complications in pre-existing lesions[14]. As atherosclerosis is defined as a progressive disease, characterized by the accumulation of lipids, fibrotic material, and inflammatory elements, specifically in response to vascular endothelial injury[14-16], it is associated with mechanical causes such as arterial hypertension, exogenous toxins such as those found in tobacco, abnormally glycosylated proteins associated with diabetes mellitus, lipids or proteins modified by oxidation, and possibly viral and bacterial infections[14,17,18].

On the other hand, regular physical activity can improve cardiovascular risk, reduce plasma triglycerides, and increase high-density lipoprotein cholesterol (HDL-C)[19]. In addition, it reduces blood pressure[20],

improves glucose metabolism and insulin sensitivity[21], and reduces body mass and inflammatory markers[22]. Other benefits include improved endothelial function[23], increased vagal tone associated with a lower heart rate[24], vascular remodeling including larger vessel diameters and an enhanced nitric oxide bioavailability[25]. Therefore, these improvements in risk factors may explain the reduction in CVD[26].

The physical activity of athletes does not prevent the development of central and peripheral atherosclerosis[27]. The mechanisms leading to increased coronary atherosclerosis in athletes are largely unknown, but there are potential pathways, although speculative, that may link exercise training to CAC and plaque development[28].

Catecholamines increase heart rate and cardiac contractility during exercise. The exercise-induced increase in cardiac output may increase mechanical stress on the coronary vessel wall and disrupt laminar blood flow patterns, leading to vessel wall injury and premature atherosclerosis[29]. High blood pressure can accelerate atherosclerosis[30]. The finding that vigorous-intensity physical exercise is associated with higher prevalence of CAC and atherosclerotic plaques fits this hypothesis, as more intense exercise is associated with increases in both heart rate and systolic blood pressure[5].

The effects of exercise on vitamins, minerals and hormones may also influence the association between exercise and coronary atherosclerosis. Serum vitamin D concentrations are inversely related to CAC[31,32] and may accelerate atherosclerosis in athletes with vitamin D deficiency[33]. Similarly, magnesium can prevent vascular calcification via multiple mechanisms[34], and serum magnesium concentrations are inversely associated with CAC[35], whereas athletes may have low concentrations of magnesium[36]. Parathyroid hormone increases during exercise[37], which probably suggests a decrease in ionized calcium concentration during exercise. The reason of the reduction in serum concentration of calcium is unknown, as well as its destination[38]. However, higher levels of parathyroid hormone are associated with greater atherosclerotic disease burden[39]. Repeated exposure to higher levels of parathyroid hormone after exercise can therefore accelerate coronary atherosclerosis in athletes[28].

Inflammation plays an important role in the development of coronary atherosclerosis and physical exercise modulates inflammation[40]. Long-term exercise lowers inflammation[41], but acute exercise may increase inflammation[42]. Although there is a large body of evidence supporting a suppression of inflammation in athletes, high-intensity, frequent, and prolonged exercise can produce an inflammatory effect, accelerating coronary atherosclerosis[28].

Given the relationship between strenuous physical exercise and CAC, it is observed that calcification is associated with instability, which may influence plaque disruption[43]. However, calcium accumulation may be associated with low risk of thrombosis[44]. That said, vascular calcification is a relevant pathophysiological process that is associated with coronary atherosclerosis and pathophysiological changes such as decreased vascular compliance and increased pulse pressure (due to increased systolic blood pressure and reduced diastolic blood pressure), in addition to changes in flow distributon and loss of self-regulation mechanisms[45]. In general, four mechanisms of calcification were identified (Table 1).

Table 1 - Calcification mechanisms[44]

Calcification mechanisms	
1	Death of inflammatory cells and release of apoptotic bodies and necrotic debris from the atheroma, which serve as nucleation sites for the formation of calcium phosphate crystals;
2	Circulation of complexes that serve as sites for the crystallization of calcium;
3	Reduced local expression of inhibitors of mineralization;
4	Induction of bone formation resulting from differentiation of pericytes and/or vascular smooth muscle cells.

Among the processes mentioned, vascular calcification itself includes active and passive mechanisms. Active vascular biomineralization involves cellular mechanisms and leads to organized calcified tissue. It is regulated by local cells such as: intimal vascular smooth muscle cells, derived from the media, pericytes and similar cells, which differentiate into an osteoblastic phenotype. On the other hand, passive calcification is a process that is independent of cellular activity, as it results from the deposition of calcium and phosphate ions and leads to "'amorphous calcification"[46]. However, this process occurs in the absence of calcification inhibitors (matrix Gla protein and fetuin-A), leading to calcium overload and consequently to the formation of microcalcifications. Thus, at pro-osteogenic conditions, vascular smooth muscle cells continue to differentiate into a chondrocyte/osteoblast phenotype[44].

Vascular calcification can be classified into two distinct forms, depending on its location (Table 2).

Table 2 - Classification of vascular calcification according to its location[47]

Location of vascular calcification	**Associated condition**
Tunica Intima	It is the dominant type of calcification seen in coronary arteries.
Tunica Media	It is commonly observed in patients with peripheral vascular disease. It mostly affects the peripheral arteries of the lower extremities, resulting in the loss of elasticity.

Coronary artery calcification is concomitant with the development of advanced atherosclerosis. Pathologically, it begins as microcalcifications, from 0.5 to 15.0 mm, and grows into larger calcium fragments. These calcification fragments and sheets can be easily identified by radiography, as well as by computed tomography and intravascular imaging[48-50]. Coronary atherosclerosis can be evaluated by two different computed tomography protocols. Non-contrast computed tomography can show the amount of coronary artery calcification (CAC), which is expressed as CACS score (CACS) in Agaston units[55]. And coronary computed tomography angiography (CCTA) uses contrast to assess luminal stenosis, plaque characteristics, and plaque volume. Luminal stenosis can be visually graded and significant stenosis (>50%) is strongly associated with cardiovascular events[52]. Both CACS and CCTA produce results capable of predicting future cardiovascular events[53].

Radiological evaluation allows determining plaque morphology and dividing plaques into calcified, non-calcified and mixed plaques (calcified and noncalcified parts)[54]. Calcified plaques are considered stable and less prone to rupture and are associated with a lower risk of adverse coronary events, including mortality. In contrast, mixed plaques are rich in lipids and more vulnerable to fissures and subsequent thrombosis. However, the same stable calcified plaques may cause sufficient coronary stenosis and ischemia to produce myocardial scarring and fatal arrhythmias in some athletes[4].

After analyzing these data, the apparent paradox of increased coronary atherosclerosis despite lower cardiovascular risk and increased longevity in more active individuals or athletes can be explained by observations of a more benign plaque morphology in combination with beneficial exercise-induced coronary adaptations[3]. Increased physical activity and cardiorespiratory fitness seem to reduce the cardiovascular risk of CAC. This reduction may occur due to increased coronary blood flow by the combined augmentation of epicardial coronary artery diameter, vasodilator capacity, capillary density and vasomotor reactivity produced by physical exercise[55-57]. Coronary atherosclerotic plaques associated with increased volume of physical activity may also be more stable and less prone to rupture, since the most active athletes had fewer mixed plaques and more often only calcified plaques[4,5], which are associated with a lower risk of cardiovascular events[58-60].

CONCLUSION

Endurance athletes are more predisposed to increased coronary artery calcification than less active or sedentary individuals. However, it is observed is that higher lifelong exercise volumes seem to be associated with more benefits than cardiovascular risks.

Participation of the authors: *Canevazzi GJ* – Responsible for the conception of the study, analysis and interpretation of data and writing of the first version of the manuscript; *Carmo AB* - Responsible for the review and submission of the article; *Almeida FS* – Responsible for the analysis, interpretation of the data and contribution in later versions of the manuscript; *Badessa MPS* – Responsible for the critical review of the study; *Braga PG* – Responsible for planning, analysis, interpretation and writing of the study; *Sobral MLP* - Responsible for reviewing the original text and guiding the study. All authors approved the final version.

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