Title:

Inflammation and coronary artery disease: the exercise paradox

Running Head:

Exercise and inflammation

Author:

Fabian Sanchis-Gomar, MD, PhD[a,b], Carmen Mayolas-Pi, PhD[c], Nuria Garatachea, PhD[c,d,e,f]

Affiliations:

[a]Leon H. Charney Division of Cardiology, New York University School of Medicine, New York, USA

[b]Department of Physiology, Faculty of Medicine, University of Valencia and INCLIVA Biomedical Research Institute, Valencia, Spain

[c]Faculty of Health and Sport Sciences, University of Zaragoza, Huesca, Spain

[d]GENUD (Growth, Exercise, NUtrition and Development) Research Group, University of Zaragoza, Zaragoza, Spain

[e]Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y Nutrición (CIBER-Obn), Madrid, Spain

[f]Instituto Agroalimentario de Aragón (IA2)

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Author for correspondence:

Nuria Garatachea, PhD

University of Zaragoza

Faculty of Health and Sport Science

Ronda Miseridordia s/n

22001 Huesca - Spain

E-mail: nugarata@unizar.es

To the Editor,

Cwikiel et al. [1] evaluated the inflammatory effects of exercise in patients with and without coronary artery disease (CAD). They reported that patients with symptoms suggestive of CAD showed an altered inflammatory response after acute strenuous exercise. In this regard, Spender et al. [2] also studied the effects of long-term physical activity (PA) on the circulating soluble receptor of advanced glycation end products (sRAGE) levels, finally showing that its levels significantly increased after long-term PA. The authors concluded that the increase in sRAGE circulating levels may represent a marker of an advanced glycation end products-mediated inflammation, playing thus an important role in cardiovascular disease (CVD) prevention by exercise and being partly mediated by an increased inflammation status [2]. Interestingly, Laddu and co-workers recently evaluated the prevalence of coronary artery calcification after 25 years of PA [3]. Succinctly, the authors followed-up with 3,175 participants over 25 years and concluded that the most active population, that is those exceeding 3 times the PA recommended in the guidelines of 150 minutes of moderate-intensity exercise or 75 minutes of higher-intensity exercise weekly, have a higher probability of developing coronary subclinical atherosclerosis by middle age. Likewise, Merghani et al. [4] also recently reported that athletes who practiced high-intensity endurance exercise for a long time showed a higher prevalence of calcic coronary plaques and atherosclerotic plaque despite the absence of cardiovascular risk factors. It is important to emphasize that the tendency for plaque was calcified rather than mixed, and hence more benign.

Increasing evidence connects inflammation with atherothrombotic disease [5]. In effect, novel findings reinforcing the central role of inflammation in CAD have also been recently published. Specifically, a manuscript published in *The New England Journal of Medicine* using the randomized trial CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study), brilliantly reported on the potential role of inflammation in CAD [6]. Ridker et al. [6] reported that blocking the interleukin-1β inflammatory pathway while administering canakinumab had atheroprotective properties and decreased cardiovascular risk. The importance of these findings have subsequently been underlined since they may represent a novel path to prevent and/or treat certain types of CVDs for a specific patient subset [7]. Specifically, the use of canakinumab has been suggested in postmyocardial infarction (MI) patients with elevated levels of high sensitivity C-reactive protein (hsCRP) despite optimal LDL cholesterol–lowering therapy [7].

It is well-known that exercise is one of the strategies most recommended to prevent CVDs. Remarkably, chronic systemic inflammation seems to be among the pathophysiological mechanisms of this phenomenon [8]. Nonetheless, it is unquestionable that light-to-moderate

exercise is a therapy to prevent CVDs with only minor side effects. In effect, PA and exercise are highly recommended, and extensively used, in cardiac rehabilitation because of their positive impact on mortality of patients following MI. Thus, all of the evidence above raised the question of whether, depending on the subject characteristics and/or underlying disease, there is any exercise-induced inflammatory threshold to achieve the higher cardiovascular benefits of exercise and prevent the possible adverse cardiovascular effects. In such case, exercise should be doubtlessly considered as precision medicine.

Conflicts of Interests: The authors declare that they have no conflict of interest.

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