Atherosclerosis biomarkers and resting heart rate: Active players or simple bystanders?

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DOI: 10.33963/KP.a2022.0215

Received:
September 6, 2022

Accepted:
September 7, 2022

Early publication date:
September 14, 2022

The resting heart rate (RHR), often referred to as cardiac frequency at rest, is perhaps one of the most accessible and clinically informative measures that can be taken. The normal reference range of this biological measure at rest is typically between 60 and 100 beats per minute (bpm) in healthy adult people, with values below or above such thresholds referred to as bradycardia and tachycardia, respectively [1]. Frequently, the RHR can decrease below 30 bpm in people with good physical condition, especially in physically active individuals and in the elderly [2], whilst it tends to be higher in women, in overweight subjects, and in the presence of a kaleidoscope of pathological conditions [3].

Convincing evidence has emerged that increased RHR may significantly predict the risk of death, especially in patients with cardiovascular disease (CVD) [4]. Thus, the RHR can be considered a "potentially modulable" risk factor since the cardiac frequency at rest can be straightforwardly lowered by enhancing the overall volume of aerobic exercise activities [5]. In a recent article published in this issue of the journal, Jiang and colleagues carried out a cross-sectional study in which plasma soluble low-density lipoprotein receptor-related protein-1 (sLRP1), soluble receptor for advanced glycation end products (sRAGE), and apolipoprotein E (*APOE*) gene polymorphisms were assayed in a cohort of nearly 1000 apparently healthy adults aged ≥40 years [6]. The most interesting finding was that both plasma biomarkers were significantly associated with the RHR after multiple adjustments for lifestyle, medical history, age, sex, and body weight, as well as for arterial blood pressure, glycemia, plasma lipids, and *APOE* genotype. This allowed the authors to conclude that the positive interplay between sLRP1 and sRAGE plasma concentrations and the RHR may represent a novel and intriguing mechanism influencing the development and/or progression of atherosclerotic disease.

The first important reflection that we could make on this finding is that it has been known for decades that an elevated RHR may be associated with CVD mortality, myocardial infarction, and stroke [7], as well as with numerous CVD risk factors, including hypertension, an atherogenic profile of plasma lipids, and hyperglycemia [8, 9]. It is hence predictable that an atherogenic plasma profile may significantly contribute to accelerating atherosclerosis, enhancing arterial impedance, and triggering other autonomic disturbances that may augment cardiac frequency at rest. To this end, it is also not surprising that increased values of both sLRP1 and sRAGE may be associated with an increased RHR. sLRP1 is an endocytic receptor, a member of the low-density lipoprotein (LDL) receptor family, which have important functions in lipoprotein metabolism and whose increased concentration is positively associated with the risk of ischemic syndromes due to its role in triggering inflammation, vascular remodeling, and even foam cell formation [10]. Similarly, impaired sRAGE clearance may cause their accumulation within the arterial wall, thus strongly fostering oxidative stress and LDL

accumulation, and ultimately leading to progression of atherosclerosis [11]. Therefore, the most important evidence that emerged from the study of Jiang and colleagues is that the concentration of both these atherosclerosis biomarkers may have an impact on the RHR independently from other well-known CVD risk factors, which would reflect an active role played by these two factors in influencing cardiac frequency and then promoting atherogenesis in apprently healthy subjects.

Nonetheless, the crucial questions that emerge here and now, irrespective of an active or passive role played by these two biomarkers in modulating atherogenesis, are (1) whether their assessment may be worth — more specifically cost-effective — in baseline estimation of the CVD risk and (2) whether specific therapeutic interventions shall be planned for targeting their eventually increased concentration in plasma. As concerns the former instance, the measurement of both sLRP1 and sRAGE appears challenging, expensive, low-throughput, and time-consuming in routine clinical laboratories (i.e., substantially based on enzyme-linked immunosorbent assay kits), where routine lipid testing (i.e., cholesterol, triglycerides, lipoprotein fractions) using fully-automated instrumentation would be easier, faster and cheaper, giving also a much greater yield in terms of CVD risk prediction [12]. Moreover, since sLRP1 and sRAGE may exert their final effect influencing the RHR, monitoring cardiac frequency using accurate portable devices appears simpler and perhaps even more clinically predictive [3].

Concerning possible therapeutic options for targeting sLRP1 and sRAGE, these most likely encompass drugs already used to lower CVD risk. For example, sLRP1 concentration could be consistently reduced by common hypocholesterolemic drugs like statins [13], while sRAGE treatment is still in embryo, with some promising results that emerged in patients taking statins and insulin-sensitizing medications [14]. Since most sLRP1and sRAGE-modulating agents are already part of standard care for patients at increased baseline risk of CVD, investing further efforts to identify additional medications tailored to specifically target these molecules seem unwarranted according to the current biological and clinical evidence. Even considering the intriguing association between these two biomarkers and increased RHR, which emerged from the study of Jiang et al. [6], directly targeting cardiac frequency with simple and safe interventions, such as enhancing the practice of physical exercise and dietary supplements (e.g., omega-3 fatty acids) [15], seems a more practical, safe and sustainable strategy.

In conclusion, although Jiang et al. have, indeed, provided an interesting contribution to unraveling additional aspects linking the puzzling and still partially unresolved relationship between HR, CVD, and mortality, further evidence would be needed before this intriguing link can have an effective translation into routine clinical practice.

Article information

Conflict of interest: None declared.

Funding: None.

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