

Effects of physical inactivity in cardiovascular biomarkers

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Abstract: Following the currently accepted definition, a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention”. In consideration of the various important characteristics requested, in several pathologic conditions the search for the “perfect” biomarker is still ongoing. The strong association between physical activity (PA) and cardiovascular health has been well characterized and strongly established in many studies although the pathophysiology of this association is still partially unclear and worthy of further investigations. Different types of biomarkers associated with cardiovascular disease (CVD) risk have been assessed in various studies and discussed in the review. The exercise-induced changes on cardiovascular biomarkers requires further studies through focused Randomized Clinical Trial in order to provide stronger and globally accepted piece of evidence regarding this field.

Keywords: Regular physical activity; vascular damage; cardiovascular disease (CVD); atherosclerosis; myokines; cardiovascular biomarkers

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Introduction

It is well established the concept that regular physical exercise induces stable physiological and metabolic adaptations for several cells, tissues and organs, including the cardiovascular system. Exercise training has a relevant role in healthy growth and aging, a great beneficial effect on overall mortality and can prevent the occurrence of many chronic diseases, as extensively discussed in several excellent papers (1-4).

A physically active behavior is reported to increase 8–10 years of life free from chronic limiting illness in comparison to sedentary lifestyle (5) also for low-intensity programs: 92 minutes per week or 15 min a day of moderate-intensity endurance training have been reported to provide a 14%

reduced risk of all-cause mortality and 3 years longer life expectancy (6). A light-intensity exercise program, such as fast walking, has provided good level of evidence to be adequate to improve blood pressure control in individual with essential hypertension (7), although in a different extent in relation to different patterns of nocturnal fall of blood pressure (8), may improve some metabolic parameters (9) and risk factors in type 2 diabetes (10), may help to control low-level systemic inflammation (3), a key factor linking physical inactivity (PI), unhealthy lifestyle and future development of multimorbidity (11-13).

Even a very low amount of exercise, quantified in 5 to 10 minutes of running/day also at slow speed (<6 miles/hour) has been associated with markedly reduced risk of death from all causes as well as cardiovascular disease (CVD) (14).

Unlike drug therapy, physical activity (PA) has few side effects and it is a cost-effective means for prevention and treatment (15), properly compared to a “polypill” (16,17).

The current enormous worldwide high prevalence of sedentary lifestyle is the consequence of progressive modernization and automation occurred during the last century, favoring the shift to more sedentary occupational tasks and lifestyle. This sedentariness has been described as a major mortality risk factor, independent of PA and ~5.3 million deaths are attributed to PI (1) which is, in fact, the fourth leading cause of death worldwide (18).

As suggested by Tremblay *et al.* in 2017, the social and economic burden created by these changes in our lifestyle, gives rise to the urgency for clear, common and accepted terminology and definitions (19). While the term *PA* has been well established in literature for many years and is currently still defined as Caspersen *et al.* suggested in 1985 as “any body movement generated by the contraction of skeletal muscles that raises energy expenditure above resting metabolic rate, and is characterized by its modality, frequency, intensity, duration, and context of practice” (19,20) the definition of both PI and *sedentary behavior* has seen some updates during the last years.

PI is defined as “the failure to meet a predefined moderate to vigorous-intensity PA threshold” (1) while *sedentary behavior* is defined as a “behavior characterized by an energy expenditure ≤ 1.5 METs, while in a sitting, reclining, or lying posture” (19).

As we can grasp from these definitions, it is important to underline that PA and sedentary behaviors are not the opposite of each other: individuals are considered to be active when they reach PA recommendations for their age, which does not prevent them from also devoting a significant part of their time to sedentary behaviors (1).

As for the difference between PI and *sedentary behavior*, even if in 2012 the Sedentary Behavior Research Network proposed a more accurate and widely accepted clarification there still remains a need for further consensus. In fact the standardized use of these key terms has had variable uptake across disciplines and medical subject headings continue to use PI when sedentary behavior would be more appropriate (19).

In conclusion, given the epidemiological importance of PI as a modifiable risk factor for morbidity and mortality and the consequential need for suitable diagnostic and follow-up tools, we aimed to review the effects of PI on cardiovascular biomarkers.

The concept of cardiovascular biomarker

Following the currently accepted definition, a biomarker is “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (21).

According to this definition, a biomarker may be a metabolic indicator searched in a biological sample (urine, blood, or biopsy), but may be also derived by an instrumental examination (e.g., blood pressure measurement, electrocardiogram registration, 24-h Holter analysis, analysis of data obtained through echocardiogram or computed tomography scan) (22).

In several pathologic conditions the search for the “perfect” biomarker is still ongoing because an useful biomarker have to grant to the clinician different important characteristics: (I) accuracy; (II) reproducibility; (III) standardization; (IV) easiness to detect and to interpret by clinicians; (V) high sensitivity and specificity for the outcome it is expected to identify; (VI) well accepted by the patient; (VII) high positive predictive value independently of established predictors for the expected outcome (23).

Biomarkers are a powerful tool requiring rigorous and critical interpretation. Their use can help physicians to classify individuals into categories of disease or no disease, to determine the risk of an event or prognosis as well as to target interventions in clinical practice (24). In order to properly use biomarkers, distinction between a causal factor and a biomarker must be taken into consideration: to be useful, a biomarker need not contribute directly to the disease mechanism (24).

Considering the variety of uses, the desirable characteristics of a biomarker differ with their intended utilization: biomarkers of screening, high sensitivity and specificity, predictive value, large likelihood ratios, and low costs; yet, for biomarkers monitoring the response to therapy, features such as narrow intraindividual variation and association with disease outcome are critical (25). The search for the “perfect” biomarker is challenging in various scientific fields.

CVD is a leading cause of death worldwide and continues to increase in prevalence compared to previous decades, in part due to the aging of the world population (26,27). Identification of biomarkers with high sensitivity and specificity for assessing the prognosis of CVD is thus necessary for optimizing personalized treatment and reducing mortality (28,29). Although over the past 30 years

Table 1 Cardiovascular biomarkers in clinical practice: the main indicators from *biological sample*

Type of biomarker	Discussion	Reference
Lipid-related biomarkers	LDL-C is a major risk factor for the development of coronary artery disease. HDL-C's protective role has now been brought into question by negative findings from clinical trials of drugs that increase high-density lipoprotein cholesterol and by negative Mendelian randomization studies. Novel lipid-related markers, including serum levels of proprotein convertase subtilisin/kexin type 9, oxidized phospholipids and secretory phospholipase A2 have also recently been shown to be associated with a risk of developing coronary artery disease in the general population	(31)
Inflammation-related biomarkers	hs-CRP and fibrinogen are the most commonly used inflammation-related risk factor. High sensitivity C-reactive protein (hs-CRP) is the most extensively studied biomarker, data regarding hs-CRP and cardiovascular risk, though largely consistent, are of unclear clinical relevance. In summary, as assessed by the Emerging Risk Factors Collaboration in 2012, the additional assessment of CRP or fibrinogen in people at intermediate risk for a cardiovascular event could help prevent one additional event over a period of 10 years for every 400 to 500 people so screened	(32,33)
Myocardial-stretch related biomarkers	Several studies have shown an association between either NT-proBNP or BNP with cardiovascular events. NT proBNP, which is a more stable form of BNP, is also predictive of a diagnosis of heart failure. Medications and other therapies utilized currently to treat heart failure are also known to reduce BNP levels effectively although with some exceptions. In order to correctly interpreted the results it is also important to understand that BNP levels are inversely associated with obesity, and may also be influenced by presence of kidney disease	(25,26)
Cardiomyocyte necrosis related biomarkers	High sensitive assays of Troponin T and I, are mainly used in detection of myocardial ischemia but are also elevated in the blood of patients with severe heart failure and therefore have been appropriately studied for the prediction of heart failure and for prognostication in those with established heart failure	(26)
Myokines (Irisin, follistatin-like protein 1) (FSTL1)	Several myokines seem to play an essential role in the protective effects of heart functions through metabolism regulation, such as irisin and follistatin-like protein1 (FSTL1) and have been reported to be considered as a therapeutic approach to improve myocardium metabolism and cardiac regeneration. Measurements of myokines in the context of heart failure and/or CV diseases might be adopted to assess the risk of adverse cardiovascular events	(34)

Summary on the main biomarkers obtained from biological sample and frequently used in clinical practice. The biomarkers are grouped by the pathological process which they represent. The discussion is based upon the most recent data available in literature.

advances in biomarker research and developments related to CVD have led to more sensitive screening methods, earlier diagnosis and improved treatments resulting in more favorable clinical outcomes in the community, the use of biomarkers for different purposes in cardiovascular remains an important area of research and many new developments are still underway (26). For example, in recent years, the physiological and pathological effects of *exosomes* on CVD have been extensively studied and accumulating evidence. It has been suggested that cardiomyocyte-derived exosomes not only play an important role in the progression of CVD (30) but have also been proved to be accessible in nearly all body fluids and reflect disease stage or progression (28).

In summary, there are numerous cardiovascular biomarkers that are currently available and that have clinical use as diagnostic, prognostic or predictive (26) and,

although risk in CVD is still determined predominantly by clinical factors, biochemical, cellular and imaging parameters is steadily allowing for incrementally refined risk assessment and, over time, this is gradually moving us nearer to the paradigm of targeted, precision medicine (31).

A detailed review of both well-known and under study cardiovascular biomarkers is beyond the scope of this review. Nevertheless, given the extent of data at our disposal, an overview of the most important CV biomarkers used nowadays in clinical practice, seems necessary.

Biomarkers can be grouped following different criteria (e.g., disease-specificity, use in clinical practice, pathologic process) (26). *Table 1* summarizes the main cardiovascular biomarkers used in clinical practice, grouped based on the pathological process they represent.

As for instrumental biomarkers, the available data are

Table 2 Cardiovascular Biomarkers in clinical practice: the main *instrumental* risk markers

Biomarker	Discussion	References
Systolic and diastolic blood pressure	Office, ambulatory and blood pressure (BP) measurements have increasingly been applied in clinical practice and research as they provide a comprehensive assessment of cardiovascular risk related to hypertension in a variety of clinical settings	(38)
Coronary artery calcium (CAC)	Yeboah <i>et al.</i> in 2014 for the first time described CAC as a tool for refining cardiovascular risk prediction in individuals classified as intermediate risk by the Framingham Risk Score or the Reynolds Risk Score	(37)
Carotid intima-media thickness (CIMT)	Nambi <i>et al.</i> in the ARIC (Atherosclerosis Risk In Communities) study showed that adding plaque and CIMT to TRF improves CHD risk prediction	(39)
Ankle-Brachial index (ABI)	Fowkes <i>et al.</i> showed in a meta-analysis that ABI is an independent predictor of incident CVD. Measurement of the ABI may improve the accuracy of cardiovascular risk prediction beyond the Framingham Risk Score	(40,41)
Brachial flow-mediated dilation (FMD)	Yeboah <i>et al.</i> showed that brachial FMD is an independent predictor of incident cardiovascular events in population-based adults. Even though the addition of FMD to the Framingham Risk Score did not improve discrimination of subjects at risk of cardiovascular disease events in receiver operating characteristic analysis, it improved the classification of subjects as low, intermediate, and high CVD risk compared with the Framingham Risk Score	(42)

Summary of the main biomarkers obtained from the most validated instrumental analysis, frequently used in clinical practice. The discussion is based upon the most recent data available in literature. CVD, cardiovascular disease.

fewer. In this field, instrumental risk markers that have shown promise in cardiovascular risk assessment are: coronary artery calcium (CAC) (35,36), carotid intima-media thickness (CIMT), ankle-brachial index (ABI), brachial flow-mediated dilation (FMD) (37).

Table 2 shows the main instrumental biomarkers according to available information.

Consequences of physical inactivity for human health

Regular exercise is without doubt a powerful and extraordinary simple way to treat and prevent a wide range of chronic pathological conditions, such as metabolic diseases related to obesity, atherosclerotic degeneration of vessels and related vascular events, other CVDs, neurodegeneration, cancer, and several others (12).

So, how does PA influence our body “well-being” and, consequently, how does the lack of it, influence its “malaise”? Exercise biology is complex, and it involves various metabolic and molecular changes that translate into changes in substrate utilization, enzyme activation, and improvement in exercise performance (43). Various mechanism underling these effects have been proposed and only partially understood: enhanced nitric oxide-mediated

vasodilation and optimized shear stress are main benefits together with oxidative stress modulation and the putative anti-inflammatory effect of exercise (29,44).

Recently, it has been proposed that the protective effects of PA could also be attributed to the muscular production of peptide mediators called *myokines*, these, secreted during skeletal muscle contraction, may trigger specific metabolic pathways in different tissue and organs far from the muscle allowing the latter to communicate with many organs such as visceral fat, bone, liver, and nervous system, among others (29). As for the pathophysiology of this “communication”, accumulating data suggest that some myokines may work exerting specific endocrine effects on visceral fat or mediating direct anti-inflammatory effects and some other may work locally within the muscle via paracrine mechanisms, exerting their effects on signaling pathways involved in fat oxidation (45).

PI dysregulates molecular circuitry, thus influencing the development of the different pathologic conditions up to determine its clinical expression (2). The exact underlying biochemical and molecular mechanisms of PI are not well characterized. Yet, as asserted by Booth *et al.*, it is important to remind that these mechanisms are not simply the converse of PA; instead, mechanisms of PI in some cases employ totally different pathways than PA uses (46,47).

PI interacts with other environmental factors to increase risk for many chronic conditions and represents an actual cause of premature death (47). PI impacts on the pathogenesis of so many diseases so much that, in order to indicate this cluster of diseases, Pedersen suggested the term “diseasome of PI” (48). In fact, PI appears to be an independent and strong risk factor for accumulation of visceral fat, which again is a source of systemic inflammation (48) and is recognized as one of the leading risk factors for developing of at least 35 chronic diseases/conditions (46).

Cardiovascular health and physical inactivity

PI increases the prevalence of all major CVDs (e.g., subclinical atherosclerosis, coronary heart disease (CHD), acute coronary syndrome, angina pectoris, cerebrovascular disease, high blood pressure, heart failure) (47).

Numerous studies have established the importance of PA and fitness for long-term cardiovascular health (49) and its importance on lowering morbidity and mortality from heart disease (50).

Regular moderate exercise (i.e., as recommended by U.S. PA Guidelines, 30 minutes of moderate exercise—like a brisk walk—for 5 days per week or more) has been shown to be helpful for both the primary and secondary prevention of CVD in both men and women as well as engaging in more strenuous exercise (like jogging) for shorter periods of time, such that 15 minutes of jogging done 5 days per week (50).

On the other side, there is evolving evidence that excessive endurance exercise (defined as from 60 to 90 min Exercise Training per session), high-volume and/or high-intensity long-term exercise training, may attenuate the health benefits of a physically active lifestyle as demonstrated by the findings of accelerated coronary artery calcification, exercise-induced cardiac biomarker release, myocardial fibrosis, atrial fibrillation, and even higher risk of sudden cardiac death in athletes (51).

The mechanisms that contribute to the relationship between CVD and PI and/or sedentary behavior are still under investigation and can be grouped as direct and indirect mechanisms. The “indirect-mechanisms hypothesis” relates to the demonstrated impact of sedentary behavior on traditional cardiovascular risk factors both in healthy volunteers (52,53) and in populations with CV risk and/or CVD (54,55).

Regarding the effects exerted by PA about CV system, regular training or exercise has direct structural and functional benefits in the vasculature, including cardiac

preconditioning (56), and various indirect advantageous effects. In fact, regular PA has been demonstrated to reduce abdominal adiposity and improve weight control (57), improve lipid profile reducing triglyceride levels and increasing HDL cholesterol levels (58) improve insulin sensitivity and glycemic control in type 2 diabetes (10), grant a reduction of systolic and diastolic blood pressure both in normotensive and in hypertensive subjects (7,59), improve autonomic tone and sympatho-vagal balance (60), restore blood coagulation, fibrinolysis and platelet aggregation (61), augment coronary blood flow (62), and improve endothelial dysfunction (63). Some of these effects may be due to the muscle-derived myokines—already cited in this review, which induce a healthy anti-inflammatory milieu, and the promotion of a healthy gut microbiota (64).

Changes in cardiovascular biomarkers in sedentary subjects

Although the pathological pathways linking sedentary behavior and CVD are still unclear and under research, recently there has been an interest in understanding the biomarkers underlying the response to PA, focusing mainly on biomarker related to cardiovascular risk (65).

Numerous studies have taken under investigation the changes in cardiovascular biomarkers in sedentary subjects, sometimes with conflicting and unclear results.

Different types of biomarkers associated with CVD risk have been assessed in various studies.

Analyzing the data available (from RCT, POS and CSS), the majority of studies exploring the modification of some anthropometric-systemic markers (e.g., Body Mass Index, Waist Circumference, Systolic blood pressure, diastolic blood pressure), lipid-related biomarkers, glycemic biomarkers and sedentary behavior showed mixed evidence of association or no evidence for association: Qi *et al.* in 2015 reported that objectively measured data showed that sedentary time was not related to blood pressure or cholesterol levels or CRP levels; in 2017 Wirth *et al.* reported that the studies concerning the relationship between sedentary behavior and both systolic and diastolic blood pressure showed non-significant results (65,66).

Objectively measured data showed that sedentary time is also strongly associated with triglycerides, indices of insulin resistance, 2-hour plasma glucose (66) León-Latre *et al.* also showed a significant association between sitting time and all glycemic and insulin resistance-related parameters studied, with the exception of glycated hemoglobin (67).

Sedentary time is thought to affect glucose homeostasis and lipid metabolism by reducing muscle GLUT4 content and insulin-stimulated glucose uptake while also reducing lipoprotein lipase activity, leading to impaired triglyceride and HDL cholesterol metabolism (68) and, consequently, to a greater cardiovascular risk.

As for inflammatory-related biomarkers (e.g., CRP, IL-6, and TNF- α), these are relatively stable and rarely affected by exercise behavior (69).

Apart from these more studied biomarkers, novel ones have also been taken under consideration focusing on their modification in response to PA.

Among the most promising “novel” cardiovascular biomarkers, both BNP and NT-proBNP apparently decrease in patients with ventricular heart dysfunction who undergo exercise training (70,71).

The exact mechanism remains unclear and these promising effects remind us that these biomarkers deserve further study (69).

Brierley *et al.*, focused on how changes in sedentary behavior in workplace could positively modify cardiometabolic risk marker and, likely the cardiovascular risk; the study found that, in general, sedentary behavior workplace interventions showed promise for improving cardiometabolic risk markers, although there was no consistency in which cardiometabolic risk markers showed improvement across interventions (72).

Perspectives and conclusions

The strong association between PA and cardiovascular health has been well characterized and strongly established in many studies although the pathophysiology of this association is still partially unclear and worthy of further investigations. The exercise-induced changes in cardiovascular biomarkers require further studies through focused Randomized Clinical Trial to provide stronger and globally accepted pieces of evidence regarding this field. This could be helpful not only to establish more certainties regarding the biological pathways in which PA has a role but also to give the practitioner the instruments to better assess prognostically and to better outline the follow up of the individuals for whom the sedentariness has a major role in the deterioration of cardiovascular health and quality of life.

Furthermore, there is still the need to clarify the features of some cardiovascular risk biomarkers to have a univocal position on their actual use and utility for diagnostic, prognostic and follow-up purposes.

In conclusion, at present, the magnitude of data regarding this issue is still too “unshaped” and needs better characterization and homogenization to obtain a greater consensus and a practical application in clinical practice.

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