

Intensive exercise and its effect on the heart: Is more always better?

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Introduction

Regular physical exercise is undoubtedly beneficial for humans. Since the 1950s, numerous prospective follow-up studies have assessed both all-cause and cardiovascular (CV) mortality in relation to levels of physical activity. The results have always been unambiguous. Both men and women who presented with higher levels of physical activity were found to have a reduced risk of death (by up to 50%). Noteworthy, those who maintain a physically active lifestyle but at the same time present with other risk factors for CV diseases (CVD; smoking, hyperlipidemia, hypertension, diabetes, obesity) appear to be at a lower risk of premature death than sedentary subjects without risk factors [1]. Physical activity reduces the incidence of hypertension, ischemic heart disease and CV events, type 2 diabetes, cancers (in particular colon and breast cancer) and osteoporosis [2]. Furthermore, when applied in the secondary prevention of CVD, regular physical exercise, regular physical exercise reduces all-cause mortality.

Whether for health-related reasons or not, the number of people participating in sports activities is increasing and healthy lifestyle has indeed become fashionable in the last decade. In addition, extreme forms of endurance exercise such as marathon, triathlon and ironman triathlon have become increasingly popular among amateurs. Globally, the number of marathon runners increased by 13% in 2009–2014 and 0.5% of the United States population participated in at least one marathon [3, 4]. Amateur participation in these extreme sports is

associated with the need for hours of training, often daily, and competitions are exhausting.

Thus, a question arises whether in spite of undisputable health benefits connected with physical activity, such intensive forms of endurance sport still continue to be so, or if they can adversely affect the cardiovascular system.

Is more always better?

Sports-related cardiovascular risks

Proarrhythmia

As in the general population, atrial fibrillation (AF) is the most common arrhythmia in athletes. Multiple studies indicate that the risk of AF in athletes is higher compared to non-athletes [5]. It is believed that chronic intensive physical training predisposes to this arrhythmia mostly due to the left atrial enlargement, increased left ventricular mass and increased vagal tone [6].

Metabolic changes and adrenergic activation caused by intensive exercise are known to trigger life-threatening arrhythmias in predisposed hearts, or in other words in the presence of structural heart disease. In a cohort study performed among young subjects in Veneto, Italy, the risk of sudden cardiac death among competitive (i.e. regularly training and participating in competitions) athletes was compared to that in a non-athletic population. A 2.5-fold higher risk of sudden cardiac death was shown among competitive athletes, and was related to structural heart disease including coronary artery anomalies, arrhythmogenic right ventricular (RV) cardiomyopathy or ischemic heart disease [7].

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However, even in the absence of structural heart disease, a question arises concerning possible negative effects of intense physical exercise and participation in extreme sports on the CV system.

Hemodynamics and right ventricular dysfunction

In a study among Boston marathon amateur participants, completion of the marathon was associated with increased pulmonary artery pressure, increased RV dimensions and impaired RV systolic function [8]. Imaging techniques reveal RV functional abnormalities immediately after an intensive endurance exercise. In the study by La Gerche et al. [9] in athletes who completed ultra-triathlon, transthoracic echocardiography showed significant RV dysfunction, reduced tricuspid annular plane systolic excursion (TAPSE) and reduced RV fractional area change (RV FAC). In some athletes, cardiac magnetic resonance showed delayed contrast enhancement (consistent with fibrosis) within the right-sided interventricular septum.

Intensive exercise results in a greater increase in pulmonary artery pressure relative to systemic pressure, as the pulmonary vascular bed is characterized by lower adaptive capacity which does not improve under regular training. Thus, the RV which generates the same cardiac output as the left ventricle, is subjected to greater afterload which does not decrease with repeated training. Compared with rest, the RV wall tension in athletes increases by 170% during exercise, compared to a 23% increase in the left ventricular wall tension. This may lead to RV hypertrophy and remodeling [10].

In addition to imaging techniques, also biochemical parameters and biomarkers are used to determine the effect of intensive endurance training on the RV function. A significant increase in cardiac troponin and B-type natriuretic peptide (BNP) levels observed immediately after exertion, indicated myocardial damage and were correlated with echocardiographic RV systolic dysfunction [11].

Cardiac remodeling and fibrosis

In an interesting experimental study in rats, Benito et al. [12] evaluated the effect of physical exercise on myocardial remodeling and its potential arrhythmogenic effect. Following 16 weeks of intensive training, collagen deposits that disrupted tissue architecture were identified in the RV myocardial intercellular spaces. Such changes were not detected in the left ventricle. In addition, programmed RV stimulation induced ventricular tachycardia in 42% of rats in the training group

compared to only 6% in the control group. This study suggests a proarrhythmic effect of adverse RV remodeling caused by intensive physical exercise. These observations were confirmed in a study by Ector et al. [13] in a group of well-trained endurance athletes. In these subjects, arrhythmias originating from the RV were commonly observed, even when causes other than intensive training were excluded, such as cardiomyopathy and ischemic heart disease. In addition, the presence of arrhythmias was associated with RV dysfunction. Reduced ejection fraction, increased end-systolic volume and areas of RV hypokinesis were shown by cardiac magnetic resonance imaging.

Some authors go a step further and use the term “exercise-induced arrhythmogenic RV cardiomyopathy”, suggesting that repeated, excessively intensive exercise with inadequate regeneration periods may lead to potentially arrhythmogenic structural cardiac remodeling. The thin-walled RV is more prone to volume and pressure overload generated during intensive and, in particular, endurance training, compared to the left ventricle. Microdamage to intercellular junctions may be responsible for gradual cardiomyocyte apoptosis and their replacement with fibrous tissue, leading to arrhythmogenic remodeling [14]. By analogy, mutations of desmosomal protein genes are implicated in the pathogenesis of arrhythmogenic RV cardiomyopathy, resulting in impaired RV myocardial architecture.

Proinflammation

Studies on pathomechanisms of exercise-induced myocardial damage suggest a possible role of cytokines and inflammatory responses. Post-exercise neutrophilia is a well-known phenomenon [15]. Previous studies indicated a role of proinflammatory cytokines in heart failure (endothelin-1, tumor necrosis factor-[TNF]-alpha) [16, 17] and in the risk of CV adverse events (interleukin [IL]-6, TNF-alpha) [18]. Recently, La Gerche et al. [19] were the first to show that myocardial dysfunction secondary to intense endurance exercise (as evidenced by elevated cardiac troponin and BNP levels along with a reduction in RV ejection fraction) was associated with increased blood levels of proinflammatory cytokines including TNF-alpha and IL-12p70i. Taking into account known effects of these cytokines, it may be suspected that repeated intensive physical exercise and associated inflammatory reactions may lead to fibrosis. In addition, the RV may be more involved as it is exposed to significant pressure overload during exercise.

Experimental studies show that TNF-alpha plays a major role in cardiomyocyte apoptosis along with damage and replacement fibrosis in different conditions of cardiac pressure overload [20].

The role of novel biomarkers

Although nowadays imaging techniques are crucial for evaluation of structure and function of the heart, cardiac biomarkers still remain an important field for further research. The standard laboratory analysis has remained unchanged in recent years and it involves cardiac troponin I and troponin T, creatine kinase MB isoenzyme, myoglobin and BNP. As already mentioned, exercise-induced myocardial damage causes a transient increase in concentrations of these markers in serum. In case of troponins levels, their concentrations in plasma usually normalize within 36 h following the endurance exercise [21].

Recently a number of novel biomarkers have been reported. They may play an important role in better understanding of the relationship between intensive physical exercise and the inflammatory response, particularly with regard to the RV function and proarrhythmia in response to an excessive, strenuous exercise.

Neopterin

Neopterin, a pteridine class compound, is synthesized and released by mononuclear phagocytic cells, e.g. macrophages, activated by interferon-gamma or TNF-alpha. The increased neopterin level is a marker of activation of cellular inflammatory response. Neopterin synthesis is closely linked to synthesis of tetrahydrobiopterin, a nitric oxide synthase cofactor. Thus, an increased neopterin level is observed in conditions with variable blood pressure and vascular tone [22]. Already in the early 1990s, Sprenger et al. [23] showed an association between increased neopterin levels and long-distance running. Increased urinary neopterin level following extreme exercise is indicative not only of cellular inflammatory response, but also of increased production of reactive oxygen species and reduced antioxidant levels [24].

Experimental studies showed an association between AF and increased levels of TNF-alpha which contribute to adverse structural atrial remodeling, i.e. hypertrophy and fibrosis [25]. Neopterin is a component of TNF-alpha signaling pathway and increased neopterin concentrations were observed in patients with persistent AF compared to arrhythmia-free subjects [26]. However,

further studies are needed to establish whether neopterin level is a predictor of arrhythmia induced by intensive endurance exercise.

Pentraxin-3

Pentraxin-3 (PTX3) is an interesting inflammatory cytokine in the context of studies on adverse effects of intensive endurance training on the RV function. It is a member of the long pentraxin class, contributing to humoral innate immunity along with short pentraxins (which include C-reactive protein) [27]. PTX3 is believed to play a role in atherogenesis, as it is synthesized by macrophages, endothelial cells, and vascular smooth muscle cells in response to inflammatory signals mediated by oxidized low-density lipoproteins [28]. Moreover, an association between PTX3 and AF was found. PTX3 levels in blood samples obtained from the left atrial appendage of subjects suffering from AF were significantly higher compared to peripheral blood, which may suggest an involvement of local inflammatory processes in the pathogenesis of this arrhythmia [29].

Nakajima et al. [30] found that compared with resting, plasma PTX3 level increased significantly immediately after intensive exercise. Circulating neutrophils that degranulate in response to exercise were identified as the main source of PTX3.

In the Multi-Ethnic Study of Atherosclerosis (MESA), PTX3 was implicated as a RV function marker in subjects without established CVD. The elevated PTX3 concentration correlated with increased RV mass and end-diastolic volume assessed by cardiac magnetic resonance, and higher RV mass was associated with a threefold increase in CV or heart failure-related deaths [31].

Galectin-3

Galectin-3, a lectin family protein, is released by activated macrophages and its receptors are present on cardiac fibroblasts. It is a mediator of fibroblast proliferation and thus of collagen production and fibrosis initiated by inflammatory reactions. Plasma galectin-3 level is increased in patients with acute and chronic heart failure, both those with reduced (HFrEF) and preserved ejection fraction (HFpEF). In both groups of patients, galectin-3 is considered a relatively novel biomarker indicating poor outcomes [32]. In patients with pulmonary arterial hypertension, elevated galectin-3 level was found to correlate with echocardiographic RV dysfunction and fibrosis, evaluated by levels of cardiac extracellular matrix metabolism markers, including tissue inhibitor of metalloproteinase 1

(TIMP1) and N-terminal propeptide of type III procollagen (PIIINP) [33].

Suppression of tumorigenicity 2

The ST2 protein (suppression of tumorigenicity 2) belongs to the IL-1 receptor family. Its ligand is IL-33, shown in animal models to inhibit myocardial fibrosis and hypertrophy in response to pressure overload. Thus, it has been suggested that IL-33 may exert cardioprotective effects in various CV conditions [34]. ST2 protein is present in two forms: transmembrane (ST2L) and soluble (sST2). It was shown that binding of IL-33 to ST2L counteracts cardiac remodeling induced by and catecholamines. The soluble form (sST2), being a decoy receptor, binds IL-33 and reduces its cardioprotective effects. It is released by cardiomyocytes and fibroblasts in response to their increased tension. In patients with both acute and chronic heart failure, sST2 plasma level was shown to be a predictor of mortality independently of left ventricular ejection fraction. In addition, sST2 may be useful to predict the risk of sudden cardiac death in relation to left ventricular ejection fraction [35, 36]. An association was also shown between plasma sST2 concentration and echocardiographic parameters of RV dysfunction in patients with pulmonary hypertension secondary to chronic obstructive pulmonary disease [37]. What is important, as sST2 antagonizes beneficial effects of IL-33 on extracellular matrix remodeling, an increased sST2 plasma concentration may worsen the conduction of electrical impulses in myocardium and thus predispose to the occurrence of life-threatening arrhythmias, like ventricular tachycardia or ventricular fibrillation [38].

Heart-type fatty acid binding protein

Heart-type fatty acid binding protein (H-FABP), present in large amounts in the cardiomyocyte cytosol, is involved in fatty acid metabolism. Even mild cardiomyocyte damage results in H-FABP release into the bloodstream and thus, a very sensitive and specific marker of acute myocardial ischemia. It was shown to predict mortality during one-year observation after myocardial infarction [39, 40]. High H-FABP levels were also shown to predict mortality due to acute right heart failure in patients with pulmonary embolism [41]. H-FABP measurements may also be useful as a sensitive and specific marker of poor outcomes in patients with chronic thromboembolic pulmonary hypertension, including those with previous pulmonary endarterectomy [42].

Although examined in terms of RV dysfunction, neither galectin-3, ST-2, nor H-FABP concentrations been studied in healthy subjects involved in intensive sports activities and particularly endurance exercise.

Conclusions

In summary, questions whether more intensive physical exercise is better for the CV system and whether thresholds exist, and above all, which sports activities may not be beneficial, remain unanswered. However, this issue becomes more urgent due to the mass popularity of sports activities and increasing engagement in extreme forms of endurance exercise. In addition to a multitude of evidence supporting the beneficial effects of exercise, studies also indicate a threat connected with intensive physical exercise, those being the dysfunction of RV function, fibrosis, disarray in myocardial muscle's architecture and proarrhythmic potential. Although the exact pathomechanisms of these phenomena have not been fully investigated yet, emphasis is put on inflammatory response to excessive physical exercise. PTX-3, galectin-3, ST-2 and H-FABP have already been linked with RV function impairment. Neopterin and PTX-3 have been associated with atrial fibrillation, whereas ST-2 — is associated with ventricular arrhythmia. Further studies are required but the hypothesis of a pathological inflammatory response to excessive physical exercise appears particularly compelling. The use of novel biomarkers could give further insight into these processes.

Conflict of interest: None declared

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