Intense physical exercise related to the emergent generation of cardiovascular risk markers: a review

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Running head: Physical exercise and cardiovascular risk markers

Abstract:

Objective: The present review was performed in order to bring together the current knowledge about the impact of intense physical exercise on cardiovascular function, especially on plasma levels of cardiovascular risk markers such as cardiac troponin T (cTnT), myeloperoxidase (MPO), amino-terminal pro-brain natriuretic peptide (NT-proBNP), C-reactive protein (CRP) and oxidized low-density lipoprotein (oxLDL).

Methods: Data were collected using the PubMed database. The articles were chosen for their relevance and importance in the area of interest.

Results: The literature describes numerous examples where physical exercise induces plasma variation for the markers studied. Intense physical effort increases the levels of cTnT, MPO and NTproBNP, whereas CRP and oxLDL levels tend to be decreased with regular sport activities.

Conclusions: The present literature investigation confirms the fact that intense physical exercise has an impact on the plasma variations of the five cardiovascular risk markers studied. However, practising regular exercise remains one of the first strategies for the prevention of cardiovascular disorders.

Keywords

Cardiovascular; Exercise; cTnT; NT-proBNP; Myeloperoxidase; CRP

INTRODUCTION

Cardiovascular diseases (CVD) represent the leading cause of death in the United States, as well as in numerous developed countries, ahead of cancers and accidents (35).

Nowadays, mortality due to cardiac events tends to be stabilised; this was notably allowed by the development of prevention (campaigns against obesity, smoking, sedentary lifestyle), the improvement of imaging and technologies and, eventually, modification of the diagnostic approach: use of cardiac markers. In spite of this progress, CVD incidence remains high because of the increase in life expectancy, of diabetes and obesity incidence.

The very low risk of cardiac events or sudden death after a vigorous physical effort has been described in diverse previous studies (1, 54, 66). The death incidence linked to physical exercise is more important among elderly people than among younger ones and among persons who do not practise regular physical activity (46, 47, 65). These undesirable events occur following a coronary disease which was unknown to them (14). Therefore, the American Heart Association recommends cardiovascular screening for athletes of all ages (38).

BACKGROUND

Over the past 2 decades, there has been a large interest in cardiac marker elevations, which are often seen following endurance sport events. Formerly used in the diagnostics of acute coronary syndromes (ACS), “cardiac enzymes” (such as creatine kinase (CK), aspartate aminotransferase, lactate dehydrogenase, myoglobin) are not used anymore in this framework, as they are totally lacking in cardiospecificity. Regarded erstwhile as the cardiac “gold

standard", nowadays isoform CK-MB determination is only recommended if troponin determination is not available, its cardiospecificity being affected by its presence in the skeletal muscle.

Cardiac T and I troponins (cTnT and cTnI) are currently regarded as reference markers of myocardial necrosis on the basis of their excellent sensitivity and cardiospecificity (2). New independent markers of cardiovascular risk, related to the troponins, have been developed since then. These emergent markers are likely to bring additional prognostic and diagnostic values in the estimation of cardiovascular risk. In the present review, we mention in particular several of these new markers, while studying the evolution of their plasma profile following intense physical exercise.

Indeed, it has been demonstrated that, following a lengthy and intense strain, some biological parameters (electrolytes, cardiac markers) can be modified among the participants in relation to a state of rest. In general, those values return to a normal state within 24-48 h after the exercise, which suggests that those effects are just transient. This might be explained by the relatively short half-life of studied markers, or water imbalance during and after the event.

In the next parts of the present review, the five following cardiovascular risk markers will be discussed in relation to intense physical exercise: cardiac T troponin (cTnT), myeloperoxidase (MPO), amino-terminal pro-brain natriuretic peptide (NT-proBNP), C reactive protein (CRP) and oxidized low-density lipoprotein (oxLDL).

METHODS

The articles reviewed were selected by using PubMed. In order to find them, keywords such as "cardiac troponin T", "myeloperoxidase", "NT-proBNP", C-reactive protein" and "oxidized low-density lipoprotein" associated with other keywords like "intense exercise",

"physical effort" and "sport activities" were entered in the PubMed search engine. Each article was chosen for its relevance and importance in the area investigated, in this case the impact of physical exercise on cardiovascular function, specifically on the variation in plasma levels observed for the five cardiovascular risk markers considered here. More recent articles were favoured over older ones, in order to avoid being redundant.

RESULTS AND DISCUSSION

Intense exercise and cardiac troponin T

Although the exact mechanism of cTnT release has not yet been made clear, its elevation is either due to necrosis of the cardiomyocytes (irreversible injuries), or to a transitory and reversible modification of their membrane permeability (29). It seems, however, very unlikely that a minor elevation of the cTnT rate following physical exercise is due to myocardial necrosis (44). The post-exercise release of cTnT would rather reflect a reversible injury of the membrane of the cardiomyocytes, which could be linked to a remodelling process (44). A potential physiological mechanism responsible of the release of cTnT after a physical effort has been proposed: the ventricular stretch induced by a sustained effort could stimulate integrins, proteins linking the cytoskeleton with the extracellular matrix, located in the membrane of the cardiomyocytes. The integrins could make the transport of the cytosolic fraction of troponins (3 to 8%) outside the healthy cardiomyocytes easier (6, 17).

The cTnT release from the cytosolic pool could also be due to the membrane damage potentially caused by oxidative stress (74), hypoxia (51) or transitory ischaemia (5). However, it has been demonstrated that a physical strain induces an important elevation of free radicals leading to an increased membrane leak (5, 48).

The major part of intracellular cTnT is linked with the myofibrils, complexed with cTnI and cTnC. cTnT kinetics, after acute myocardial infarction followed by a quick re-perfusion, are biphasic (26, 36). The first rapid elevation (1st peak) of the serum concentration of cTnT is related to the release of free cytosolic cTnT, whereas the continuous elevation (2nd peak) is associated with the release of cTnT which was linked to myofibrils. This 2nd peak is present until 180 hours after the first symptoms appeared (26).

From this biphasic curve, it appears that the half-life of the free cytosolic fraction is considerably shorter than that of the linked fraction. A hypothesis has been put forward that following intense physical exercise, the speed of return to the initial cTnT rate is due to the relatively short half-life (120 minutes) of the free cytosolic cTnT (49).

In the general population, an elevation above the 99th percentile of the reference population involves a bad prognosis (77), but this level is exceeded in many studies after strenuous exercise (12, 21, 44, 49). So, we think it would be interesting to follow these people in the long term from a cardiovascular standpoint to determine whether there is a relation between serum levels reached after standardized intensity exercise and the incidence of cardiac events in the long term as ACS. In the case of conclusive results, we would enjoy a new cardiovascular risk stratification tool. It has been determined that the elevation of cTnT, following a marathon, is inversely correlated with the training distance, suggesting that adaptation of the heart to intense exercise can decrease the cardiac injury (65).

Contrarily to the conclusions of Fortescue et al. (11) that the cTnT increase would be more important among young individuals, other studies do not mention any relationship to age (8,14, 32, 64). The results of Middleton et al. (43) suggest, in addition to an increased cTnT rate, a transient decrease of the systolic function and of the diastolic filling up after prolonged and strenuous exercise.

More recently, studies using an ultrasensitive troponin T (hsTnT) assay show normal distribution of cTnT in apparently healthy populations (45). So, it seems likely that cTnT elevations might be due to a physiological process rather than to a pathological one. Using this ultrasensitive assay allows the detection limit to be decreased, so it makes it possible to establish an early diagnosis of myocardial infarction in relation to the standard cTnT assay (56), the prognosis being all the better when the diagnosis is formulated as early as possible. The standard cTnT assay has a sufficient sensitivity to detect a suspected myocardial infarction but remains unable to obtain a risk stratification among patients suffering from stable chronic cardiac insufficiency (31).

Intense exercise and myeloperoxidase

MPO is an inflammation marker as well as a marker of the activation of neutrophils during an intense physical effort (69). Moreover, it is involved in LDL oxidation, infiltration of macrophages and neutrophils, unstable atherosclerotic plaque formation and plaque rupture (3, 4, 8). Due to its role in atherosclerosis, several studies have investigated the role of MPO in the monitoring of cardiovascular disease (3, 81). The MPO level is high among patients suffering from coronary disease, and this elevation is correlated with the severity of the coronary arteriosclerosis revealed by angiography (81).

Patients with a high MPO serum level have a significantly increased cardiovascular risk, even if the cTnT rate is normal. Besides, the measurement of MPO provides information about the prognosis that is superior to what can be obtained by means of traditional markers and allows identification of patients with unstable plaques before a complete microvascular occlusion (3). A study has shown an MPO elevation among 22 athletes out of 24 after running a marathon (41). An MPO rate above 350 ng/ml is linked with a cardiovascular risk (3). Fifty-eight percent of the runners reached or exceeded this limit following the effort, which suggests that

cardiac risks could be related to a long distance race. Moreover, a simultaneous increase of other cardiac markers, including cTnT and NT-proBNP, has been observed (41).

Furthermore, regular exercise of endurance allow reduction of the circulating myeloperoxidase level among individuals who are subject to cardiovascular diseases. This variation might be due to many antiatherosclerotic processes such as the improvement of NO bioactivity, decrease of oxidative stress and lipid peroxidation (57).

Intense exercise and amino-terminal pro-brain natriuretic peptide

Brain natriuretic peptide (BNP) and the inactive cleaved NT-proBNP fragment are synthesized by the cardiomyocytes. High blood concentrations reflect a high myocardial parietal tension due to the stretching of the myocytes. This stretching is caused by an increase of pressure or volume and neurohormonal activation in the case of heart dysfunction, heart failure, cardiac myopathies, acute coronary syndromes and other cardiac disorders. As a marker of heart dysfunction, BNP and NT-proBNP provide a useful tool for the diagnosis of cardiovascular disease, for the monitoring of drug therapy and for risk stratification (62).

At rest, BNP and NT-proBNP rates among sportsmen are not higher than among untrained individuals (59). Among over-trained athletes, those rates are not increased at rest (61). However, among some athletes and body-builders, whose background reveals an abuse of anabolic steroids, higher rates can be found compared to the controls. This might be the expression of possible myocardial lesions due to chronic use of anabolic steroids (72).

Physical exercise can induce modifications of the serum and plasma levels of BNP and NTproBNP among healthy athletes. Also, after intense and prolonged exercise, rates higher than the upper limit have been documented (16, 30, 42, 49, 52, 60, 65, 67, 75). The elevation of these rates has been associated with the length of the exercise and the athlete's age (30, 60). Shorter but more intense exercise also results in an increase of those markers among healthy

sportsmen and untrained individuals. However, this increase is shorter in time and does not exceed the upper reference limit among healthy athletes (62).

It is assumed that the rise of tension at the level of the myocardial walls, associated with intense exercise, is responsible for the increased liberation of BNP and NT-proBNP. In vitro an elevation of BNP expression when the cardiomyocytes are stretched has been demonstrated (80). Additionally, catecholamines seem to induce the myocardial expression of BNP (80). Cytoprotectant and growth regulatory effects of BNP have been demonstrated in vitro among animal models, which can also be assumed to exist among healthy athletes with elevation of the exercise-induced BNP rate (62).

It seems possible that the myocardial response or adaptation, both during and after exercise, could be regulated by the BNP liberation for a healthy athlete. This supposition is supported by the fact that larger elevations in NT-proBNP after a marathon were found among non-elite runners with shorter training distances than among elite runners (65).

Intense exercise and C-reactive protein

Inflammation is a critical parameter in the pathogenesis of cardiovascular disease (34). Atherosclerosis is an inflammatory affection which is mediated by macrophages; the latter accumulate forming artery plaques, are activated and release cytokines causing tissue damage (33). Several studies show that physical exercise provides cardioprotection via anti-inflammatory effects which could be dose-dependent (10, 27, 55). Physical exercise induce a short-term inflammatory response but in the long term regular physical activity induces an anti-inflammatory effect (25). hsCRP (highly sensitive C-reactive protein) can be used in order to provide a new outlook on the biological status of atherosclerosis affection. An augmented rate of hsCRP is a very sensitive marker of acute inflammatory reactions. It has been suggested that a slightly increased rate of the hsCRP level would be a new marker of

cardiac risk, especially coronary disease and myocardial infarction. Several studies reveal that a slight increase of the basic line of hsCRP among apparently healthy people is associated with a doubled risk of undergoing a second myocardial infarction. The predictive value of hsCRP has been demonstrated as being independent from that of other classical risk factors. An elevation of the hsCRP rate has also been associated with a higher risk of developing peripheral artery disease and with faster progression towards carotid artery disease (63).

Numerous studies show that regular physical activity decreases the hsCRP rates in a dose-dependent way (53). There was an inverse association between constant physical activity and inflammatory marker levels of the acute phase such as hsCRP (13, 7, 40, 58).

Actually, even leisurely activity (walking, swimming, dancing, etc.) decreases the hsCRP rates significantly. The same study reports that in the long term, daily aerobic exercises among elderly people reduce the serum concentrations of inflammatory cytokines such as hsCRP, IL-6, IL-8, and TNF-α (28). An inverse correlation clearly appears between physical activity and inflammatory marker levels. Complementary details on intensity, length and the required type of physical activity in order to soften the local inflammatory responses, for instance at the level of the arterial wall, could provide a fresh outlook on cardiovascular benefit induced by physical exercise (10).

Intense exercise and oxidized low-density lipoprotein

The oxidative modification of LDL is recognized as being a key step of initiation and progression of atherosclerosis (68). High circulating rates of oxLDL are associated with cardiovascular risk (18, 19). oxLDL are markers of the pathological process occurring at the level of the vascular wall. oxLDL stimulate collagen synthesis at the level of the smooth muscle cells (22), promote the thickening of endothelium (39), decrease the bioactivity of NO (9, 15, 70) and further the transendothelial migration of the monocytes (78), speeding up the

pathogenesis of atherosclerosis. Moreover, the circulating rate of oxLDL is inversely associated with artery elasticity (50, 71).

Following lengthy but moderate intensity physical exercise, a decrease of circulating oxLDL has been observed, simultaneously with an elevation of the serum anti-oxidant potential for a healthy trained individual (76). A study has shown that a programme of exercises covering ten months allows one to obtain, besides an elevation of the cholesterol HDL and a decrease of cholesterol LDL, a decrease of oxLDL rates, demonstrating the benefits of moderate regular sport practise in terms of arteriosclerosis prevention (73).

Now, as to intense effort, although it can be at the basis of an increase of the total plasma resistance towards oxidation, the oxidative resistance of the arteriogenesis lipoprotein fraction could be decreased (24). So, intense exercise increases the circulating rate of oxLDL. The latter being formed following the production of activated species of oxygen by monocytes, it is possible that intense physical effort is at the base of a mechanism responsible for a decrease of the following monocyte activities: mitochondrial superoxide dismutase and reduced glutathione. On the other hand, moderate physical activity would probably protect individuals against suppression of the anti-oxidative capacity of monocytes, induced by oxLDL (79).

Besides being an indicator of a bad prognosis of atherosclerosis, increased oxLDL rates are also detected among individuals suffering from chronic heart failure. So, the evaluation of oxLDL after intense exercise could allow the early identification of individuals at risk (23).

CONCLUSION

The present literature investigation confirms the fact that intense physical exercise has an impact on cardiovascular function, represented by the plasma variations of the five cardiovascular risk markers studied.

However, even if cardiac biomarkers are known to be rising after a strenuous effort, it is supported that the cardiovascular benefits due to the practise of regular physical exercise would be the first strategy of prevention against coronary disease and cardiovascular disease in general. Moreover, the fact that the respective rates tend to be modified with training support the hypothesis of adaptation of the cardiac muscle induced by physical activities, beneficial for the organism.

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