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## Can exercise be detrimental? Considerations based on determinations of cardiac troponins

### Czy wysiłek fizyczny może być szkodliwy? Rozważania na podstawie oznaczeń troponin sercowych

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#### Key words

physical exercise, cardiac troponins

#### Słowa kluczowe

wysiłek fizyczny, troponiny sercowe

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#### Summary

Physical exercise, particularly running, becomes more and more popular in the society. Physical effort is undoubtedly beneficial because it decreases the occurrence of cardiovascular diseases, diabetes, osteoporosis and depression. The most recent research indicates that any level of physical exercise is beneficial, from purely amateur walking or jogging to professional, high intensity training undertaken by sportsmen achieving the highest honors in the professional sport. However, physical exercise also has dark sides which include sudden cardiac death during exercise, potentially detrimental remodeling of the heart and the possibility of cardiac damage, which results in the increase in markers of cardiac muscle necrosis concentration. The article is focused on potential meaning of increased cardiac troponin concentration during physical exercise and discusses observations suggesting that the so called markers of cardiac necrosis not necessarily show the actual necrosis and can only be indicators of the intensified remodeling. Furthermore, even if such necrosis does occur, there is no definitive data to suggest that it is indeed associated with worse prognosis.

#### Streszczenie

Wysiłek fizyczny, szczególnie bieganie, zyskuje coraz większą popularność w społeczeństwie. Wysiłek wiąże się niewątpliwie z licznymi korzystnymi konsekwencjami zdrowotnymi, obejmującymi rzadsze występowanie chorób układu krążenia, cukrzycy, osteoporozy i depresji. Najnowsze badania wskazują, że każdy poziom wysiłku jest korzystny, od czysto amatorskiego spaceru czy joggingu po profesjonalny trening o wysokim natężeniu podejmowany przez sportowców sięgających po najwyższe laury w sporcie. Jednakże wysiłek fizyczny ma też ciemne strony, do których należą nagła śmierć sercowa w trakcie wysiłku, potencjalnie niekorzystna przebudowa serca oraz możliwość uszkodzenia serca, na co wskazuje wzrost stężenia markerów martwicy mięśnia sercowego. W artykule skupiono się na potencjalnym znaczeniu podwyższonego stężenia troponin sercowych w trakcie wysiłku fizycznego i przedyskutowano obserwacje sugerujące, że tak zwane markery martwicy mięśnia sercowego niekoniecznie wskazują rzeczywistą martwicę, a mogą być jedynie wskaźnikami bardziej nasilonej przebudowy. Dodatkowo, nawet jeśli taka martwica rzeczywiście występuje, brak przekonujących danych, że rzeczywiście wiąże się z gorszym rokowaniem osób podejmujących wysiłek fizyczny.

*Physical exercise, particularly running, becomes more and more popular. The amount of marathon runners and short-distance runners increases. Are we threatened by Filipades<sup>1</sup> fate?*

#### IS PHYSICAL EXERCISE HEALTHY?

Regular, aerobic physical exercise brings unquestionable health benefits: makes keeping a healthy body mass, bone density and muscle strength easier, lowers

<sup>1</sup>A Greek runner and messenger, who as the first one ran the marathon distance to announce the Marathon victory and warn the Athenians against Persian fleet. After delivering this message he died of exertion.

the concentration of cortisol, increases glucose tolerance and makes lipid profile better, improves cognitive functions, lowers the risk of depression, makes the quality of sleep better, increases the release of nitric oxide by vessel endothelium, increases arterial elasticity and lowers blood pressure (1).

There is a direct dependence between the lack of physical activity and total mortality due to cardiovascular diseases and neoplasms (e.g. colon carcinoma, breast cancer). In addition, the lack of physical exercise is a risk factor of coronary disease, hypertension (1), type 2 diabetes, osteoporosis and depression and mobile rehabilitation bring numerous benefits to patients with cardiac insufficiency and lengthens lifetime of patients after myocardial infarction (2).

These benefits occur in men as well as in women, in young patients as well as in old ones (3).

The intensity of physical exercise, which brings benefits, is, however, controversial. The latest recommendations of American Cardiology Association recommend for all adults to perform at least 30-minute moderate, aerobic exercise five days a week or a 20-minute intensive aerobic effort three times a week (4). In addition, the recommendations report that the shape of the exercise – benefits curve is not known, which means that the effects of a very intensive exercise are not yet discovered. Some authors suggest that the exercise dose – benefits curve has its maximum and curves at the point of a very intensive exercise (e.g. marathon training or the marathon itself), which means that such effort can bring more harm than benefits.

Latest research suggest, however, that the more the better. The research performed in Taiwan among general population showed that every 15 minutes more of exercise daily is connected with the decrease in mortality by 4% (5). Members of the runner club at the age above 50 (the average age 59 at the moment of the beginning and 78 at the end of observation): the risk of death in a 19-year observation 15 vs 34% in the control group and better quality of life. What is curious, not only was the mortality due to cardio-vascular diseases lower but also due to neoplasms and the greatest difference concerned infections as the cause of death! (3).

In addition, against the concerns, former members of Tour de France (1947-2012) – the most demanding cycling race in the world – live longer than the average for the population (6). In a retrospective cohort study 15 174 sportsmen from nine countries, who got medals in the Olympic Games in years 1896-2010, had longer life time by 2.8 years than the control group of people, who were not sportsmen (7). This effect was stronger in sportsmen performing endurance training than in sportsmen representing power disciplines. Similarly in another epidemiological research there was a longer lifespan of Olympic Games 1920-1965 participants in comparison to control group (8).

The above data suggest that even professional sportsmen of the highest level, which requires many hours of exercise exceeding the recommended pro-health values

of time and intensity, gain benefit of lengthening their life time. Does this mean that physical exercise does not bring any dangers or unbeneficial effects?

## UNBENEFICIAL ASPECTS OF PHYSICAL EXERCISE

Physical exercise, particularly very intensive one, such as long-distance running, is connected with some health threats. They may be divided into three groups: sudden cardiac death during exercise or soon after its end, heart rebuilt occurrence (so called sportsman heart) and cardiac damage (which results in function worsening and so called cardiac muscle necrosis markers occurrence in blood).

Analysis of sudden circulation stoppage cases among long distance runners revealed that it is a rare phenomenon – 0.5 in 100 000 participants (altogether 59 cases, 42 of which ended in death, in 10.9 million of runners) (9). The cases of sudden circulation stoppages were four times more frequent among marathon participants than among people taking part in a half-marathon and more frequent in men than women. The most frequent potential cause of sudden circulation stoppage in these patients was hypertrophic cardiomyopathy (in younger people) and coronary disease (in older ones). Other researches indicate that sudden cardiac death most frequently occurs in inexperienced runners, who trained relatively little (10). These data suggest that life threatening arrhythmias in people with structurally healthy hearts are extremely rare.

Undoubtedly regular physical exercise of a very high intensity favors atrial fibrillation, which occurs even ten times more frequently in professional sportsmen and in amateur runners and depends on the amount of finished marathons, which suggests dependence on the dose of effort (11).

Another threat is a so called sportsman heart (12, 13). During endurance training left ventricle in particular undergoes an eccentric growth: end-diastolic volume as well as the thickness of the left ventricle increase. The intensity of these changes depend on the training intensity. Although it seems physiological and after training termination these changes retreat, in about 20% of people the retreat to primary parameters is not total (14). The significance of this phenomenon is not entirely known.

Finally, the third unbeneficial aspect of training is heart muscle damage. After finishing long distance running in the part of runners there are late features of cardiac hemodynamic function worsening of the right as well as the left ventricle. They seem to be reversible and seem to retreat in 3-4 weeks after the run and include subtle worsening of diastolic activity and to a less extend systolic one. The significance and the frequency of these disorders are entirely not discovered (15). One of the elements of such damage is, as observed, an increase in concentration of some so called markers of cardiac muscle necrosis in blood during and after the exercise. The most frequently assessed markers are so called cardiac troponins.

## CARDIAC TROPONINS

Cardiac muscle sarcomer consists of monomers – actin, tropomyosin – and troponin complex. The last one is built of three subunits: troponin T (TnT), which anchors the whole complex to tropomyosin, troponin C (TnC), which binds  $Ca^{2+}$  ions during contraction and troponin I, which suppresses enzymatic ATP degradation giving energy to heart muscle contraction. Over 90% of troponins (cTn) are bound with tropomyosin and the rest is a free cytoplasmatic pool, probably spare. Each of these three troponins is coded by another gene. Additionally, cardiac troponins and skeletal muscle troponins are different, which is a basis for application of characteristic tests that detect them (16). The main plasma half-life of cTnT is 120 minutes, half-life of other troponins is not known.

Cardiac troponins are widely used as markers of cardiac muscle necrosis. It is believed that their presence in blood is a proof of irreversible cardiomyocyte damage – breaking of the cell membrane (16). Thus they are widely used especially in acute cardiac syndromes diagnostics. It is known, however, that their concentration increases not only during cardiac infarction but also with a fast ventricle activity (ventricular tachycardia, atrial fibrillation), in cardiac insufficiency, hypoxia, severe anemia and alimentary tract bleeding (17).

Lately it has been proved that during intense physical exercise and soon after its end the concentration of cardiac muscle necrosis markers in blood, in particular cardiac troponins, increases (18-20). Anyway, in 51% of marathon participants after its end the concentration of cardiac troponins increased (19) and 36% of runners, who finished the London marathon, had cTnT concentration fulfilling the criteria of an acute myocardial infarction diagnosis (21).

### IS INCREASED CONCENTRATION OF TROPONINS IN BLOOD OF PEOPLE PRACTICING INTENSIVE EXERCISE A PROOF OF HEART DAMAGE?

Numerous observations suggest that not necessarily:

1. Middleton et al. (22) claim that cTnT concentration increases consequently in all marathon runners with maximum increase not at the end or after the exercise but after about 90 minutes, which suggests that it may be a physiological response to the effort.

2. There is no dependence between the increase in cTn concentration and the age, sex or the degree of runners' fitness (19).
3. There is no dependence between the increase in cTn concentration and contractility disorders after running or adverse events in runners.
4. Research performed using very sensitive tests show that even healthy people have some low cTn concentration in blood, which has a characteristic and normal dispersion in general population (23).
5. It was shown that cardiac troponins may be released without breaking the cell membrane, probably from cytoplasmatic pool (24).
6. Finally, the increase in cTn concentration was found not only in sportsmen practicing very intensive exercise but also after a 30-minute intensive effort and even after a long march in untrained people! (15).

These observations show that it is not certain whether the increase in cTn in effort is an indicator of cardiac necrosis. It can as well be a result of cytoplasmatic pool of cTn release influenced by increased cardiomyocytes tension or intense rebuilt connected with the effort itself. However, even if such necrosis occurs its significance is not entirely clear. It is known that heart is and organ with the ability to regeneration (25). Perhaps the increased cTn concentration shows death of certain cardiac cells pool, probably the weakest, which is next replaced by new cardiomyocytes. These observations are particularly significant when taking the fact that, unlike pathological states (coronary disease, cardiac insufficiency), increased cTn concentration in healthy people practicing sport does not mean worse prognosis into consideration.

## CONCLUSIONS

A large amount of research and observations suggest that physical exercise, even very intense, is beneficial for health. There are also unbeneficial aspects connected to physical effort such as sudden cardiac death, structural changes in the heart and the increase in markers of cardiac necrosis concentration. These changes are, however, rare (sudden cardiac death) or their significance is not clear enough (structural changes in the heart and the increase in markers of cardiac necrosis concentration in view of physical exercise).

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received/otrzymano: 09.04.2014  
 accepted/zaakceptowano: 03.06.2014