A LITTLE EXERCISE A DAY KEEPS THE DOCTOR AWAY

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Insights

Introduction

In 1994, a pioneering exercise epidemiologist named Jeremy Morris described physical activity as "the best buy in public health for the West" [1]. Nowadays, medical students are educated with the same knowledge from the first moment they enter university classrooms. Over the past years, the health benefits of physical activity have been proven to reduce the risk of many chronic diseases such as cardiovascular diseases, diabetes, cancer and dementia [2, 3]. In honour of the theme of the current edition of RAMS, this editorial article will focus on the mechanisms of exercise-induced beneficial effects on the heart.

Myocardial infarction and reperfusion injury

In the industrialised world, cardiovascular diseases such as coronary artery disease and myocardial infarction (MI) remain a major cause of death [4]. In 80% of the cases, MI is caused by an atherosclerotic-induced thrombus [5]. The occlusion of a coronary artery leads to oxygen deprivation and ischemia in peripheral cardiac tissue. The magnitude of cardiac injury depends on the location and time of occlusion [5]. The most important therapeutic goal is to restore blood flow to the ischemic region because the extent and reversibility of the tissue damage are directly related to the duration of the ischemia [6]. During reperfusion, however, there are a number of biochemical changes that eventually will result in cell death and necrosis of the myocardium, shown in figure 1 [6]. This process of pathology is called ischemia-reperfusion (IR) injury [4, 6]. It is well established that exercise training provides protection against this type of injury by reducing cardiovascular risk factors (e.g. high blood pressure, smoking and obesity), but most importantly it promotes cardioprotection through a direct effect on the myocardium cells (myocytes) [6].

IR-induced cardiac cell death

During ischemia, oxygen supply to the mitochondria (the key organelles for the viability of human cells) is interrupted [6]. To fulfill the myocardial energy demand, cellular adenosine triphosphate (ATP) is generated via glycolysis, which is accompanied by an increase in intracellular lactate levels [6]. To compensate for the low intracellular pH, caused by the acid lactate, water accumulates in the cell, causing cellular oedema [7]. A decrease in ATP levels inactivate cellular pumps, like Na^+/K^--ATPase and Na^+/Ca^{2+}-ATPase, which are important in homeostasis [6]. In a physiological situation, Na^+/K^+-ATPase removes sodium out of the myocyte, while potassium enters the cell to maintain the resting electric potential [6]. The Na^+/Ca^{2+}-ATPase is important for muscle contraction [6]. Inactivity of these pumps results in an overload of sodium and calcium, which prevents cell repolarisation and causes contractile dysfunction [4].

During reperfusion, the damage caused by ischemia is exacerbated by the release of reactive oxygen species (ROS; a byproduct of the metabolism of oxygen) in the mitochondria [8]. This causes damage to the mitochondria. When the ATP production in the mitochondria of the myocytes is not preserved (because of the aforementioned damage), this can have two consequences: 1) during reperfusion, the outer membrane of the cardiac myocyte becomes permeable, which results in apoptosis or 2) during both ischemia and reperfusion, pores in the outer membrane of the mitochondria can open followed by mitochondrial swelling, rupture and cell death, shown in figure 2 [4].

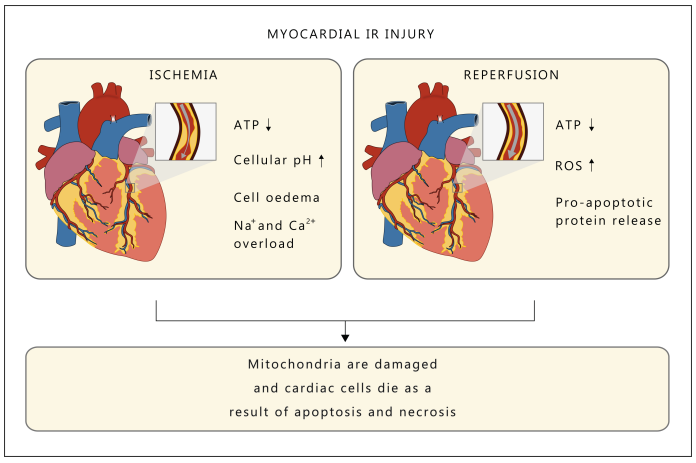

Figure 1: Mechanisms in myocardial ischemia-reperfusion (IR) injury.

Exercise and cardioprotection

Cardioprotection through exercise comprises of two phases, namely short-term and long-term cardioprotection [4]. The first phase starts 30 minutes after exercise and lasts until about three hours [4]. The mechanisms that cause this phase are not well known, but might have something to do with the activation of a specific enzyme in the cardiac myocytes called superoxide dismutase [4]. The second phase of cardioprotection is achieved within 24 hours after five consecutive days of training [9]. This effect persists for nine days [9]. Details about the dose-response impact of exercise will be discussed further on in this editorial.

Changes in coronary circulation

Exercise has the potential to increase coronary flow during reperfusion by structural changes, such as increased diameters of the arteries and arterioles [4]. However, a study performed by Bowles *et al.* on isolated perfused rat hearts showed that short-term exercise provides cardioprotection independent of improvements in coronary flow [10]. Furthermore, a previous review indicated that there is evidence that exercise directly modifies the cardiac myocyte without requiring a change in coronary circulation [4]. Cardiac myocytes isolated from the heart of exercise-trained animals are protected against IR injury [11]. These results suggest that intrinsic factors of cardioprotection may be more important that structural adaptations such as an increased vessel diameter.

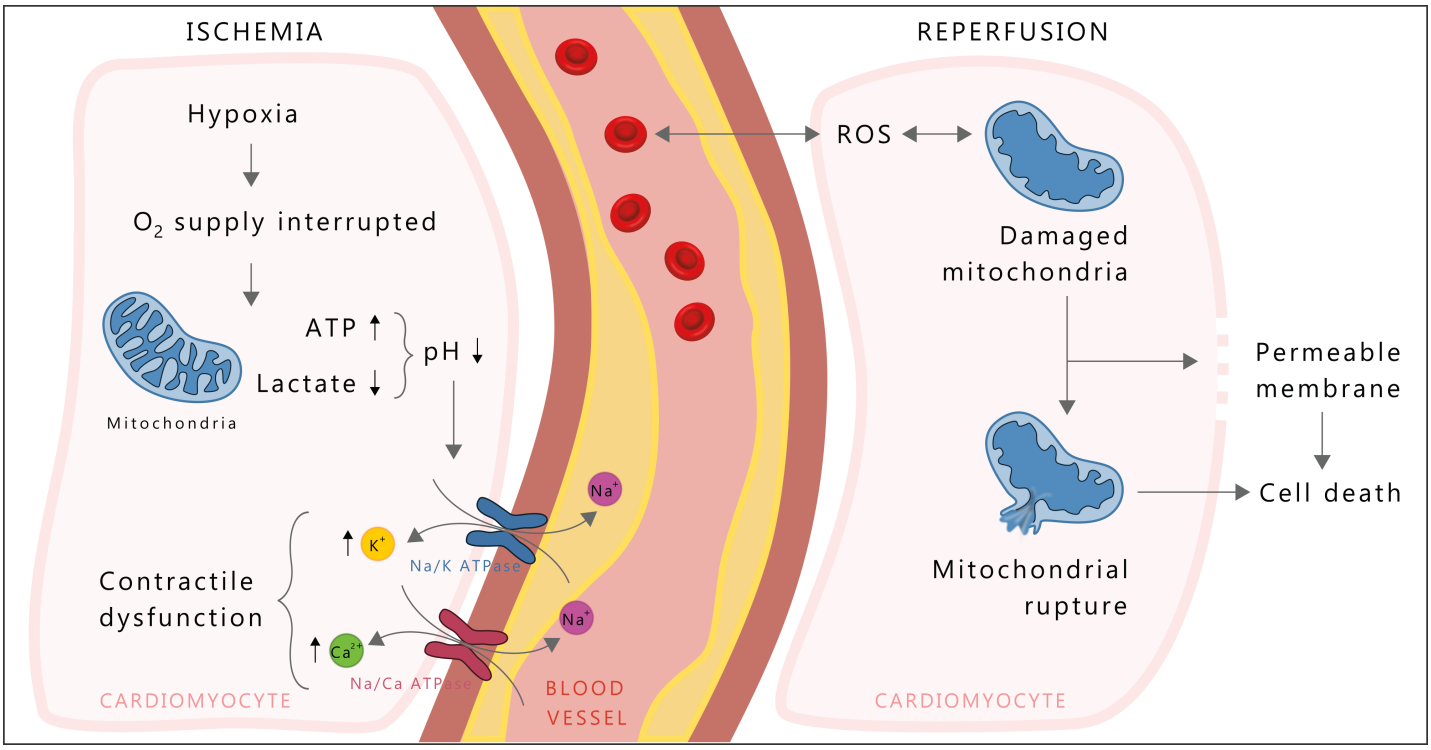

Figure 2: Cellular changes in the myocyte during ischemia and reperfusion.

Changes in mitochondria

There is emerging evidence indicating that exercise induces biochemical changes in mitochondria that are central to cardioprotection [4]. For example, exercise-trained isolated cardiac mitochondria in *in vivo* experiments by, amongst others, Kavazis *et al.* resist stimuli for apoptosis and damage induced by IR injury by not releasing pro-apoptotic proteins when exposed to ROS and/or calcium [4, 12]. Furthermore, research in mitochondrial protein expression suggested that endurance exercise leads to increased expression of beneficial antioxidant proteins and decreased expression of proteins with potentially damaging effects [4]. Taken together, exercise-induced changes in mitochondria could improve the capacity of ATP production during ischemia and may eliminate ROS during the reperfusion phase, leading to an attenuated IR induced damage [4].

Changes in the opioid system

In 1995, Howlett *et al.* discovered that morphine used to treat the pain associated with MI may also reduce the infarcted area and that the levels of beta-endorphins (an endogenous opioid agent) increase in patients with MI [5, 13]. It has been suggested that pharmacological blockade of the opioid receptors might reduce the infarcted area by 50% [13]. Stress conditions, like exercise, are known to increase the levels of opioid agents as well [6]. Immediately after a session of physical activity, the amount of opioid receptors in the heart transiently increases [14]. Although the relationship of opioids with exercise-induced cardioprotection is not studied very extensively, the acute benefits of exercise may be partially mediated by an opioid receptor-dependent mechanism [6].

How much exercise in clinical practice?

The Physical Activity Guidelines for Americans were updated in 2018, as well as the Dutch Guidelines for Exercise in 2017 [3, 15]. These guidelines indicate that adults should perform 150-300 minutes of moderate intensity or 75-150 minutes of high-intensity activity per week to gain most health benefits of an active lifestyle [3]. Most importantly, the greatest health benefits occur when changing from inactive behavior to a lifestyle with small amounts of physical activity [3]. For patients with cardiovascular disease, the American College of Cardiology and the American Heart Association guidelines from 2014 prescribe 30 to 60 minutes of moderate intensity physical exercise for five to seven days a week, apart from their daily lifestyle activities like gardening and household work [2]. The 2018 American guidelines also emphasise that the prior threshold of at least ten minutes of activity is outdated and that even brief amounts of exercise (such as climbing the stairs) are beneficial [3]. Patients thus need to know that they do not need large amounts of time to become healthier. Also, it is possible to perform all activities on one or two days per week because the health benefits from this exercise are similar to those achieved by activity on three or more days per week [16].

Conclusion

Cardiovascular diseases like myocardial ischemia are an important cause of mortality and morbidity in the Western world. One method of providing sustainable cardioprotection is exercise, but the exact underlying mechanisms responsible for this cardioprotection remain a topic of debate and research. Nevertheless, the most convincing evidence indicates that alternations in mitochondria are central in protecting the myocytes against damage from ischemia and reperfusion and that these effects might already occur during little exercise a day. It is important to take this into account, because little exercise is always better than no exercise at all.

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EXAM QUESTIONS

As RAMS aims to enlighten both students and professionals, we would like to present you two exam questions. Find out if you can remember what you have learned during your bachelor's!

We challenge you!

Question 1

During a period of abstention from food, fat storage is used. What are the resulting fatty acids mostly used for? For the production of ...

A. Alanine
B. ATP
C. Glucose

(Topic from Q3 MGZ Homeostasis, 2018)

Question 2

An electrocardiogram (ECG) is performed on a 56-year old man during a sport-medical examination. This shows a left bundle branch block. A left bundle branch block can be the result of coronary atherosclerosis. In a left bundle branch block, the ECG is characterised by ...

A. A QRS-width < 0.12 s. with a positive 'notched' QRS in lead V1
B. A QRS-width < 0.12 s. with a positive 'notched' QRS in lead V6
C. A QRS-width > 0.12 s. with a positive 'notched' QRS in lead V6
D. A QRS-width > 0.12 s. with a positive 'notched' QRS in lead V1

(Topic from Q7-Q11 KVS, 2018)

The answers to these questions can be found on page 14 in this journal.