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Editorial

When enough is more than enough: The hidden side of the cardiac effects of intense physical exercise

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Reactive oxygen species (ROS) mediate redox homeostasis and modulate several physiological cellular processes. A basal concentration of ROS is essential for normal life, but exposure to high levels of ROS contributes to the development of human disease. Enzymatic and non-enzymatic antioxidants counterbalance the effect of oxidants. Reduced glutathione (GSH) is the most abundant thiol in the cell and serves as a scavenger of ROS and reactive nitrogen species or as a cofactor for various detoxifying enzymes, such as glutathione peroxidase and transferase [1]. In addition, GSH plays a role in converting vitamins C and E in their active forms. Recently, the glutathione pool gained importance being involved in the S-glutathionylation, a reversible oxidative post-translational modification where GSH forms disulfide covalent binding with cysteine residues (P-SSG) of proteins. P-SSG raises the net negative charge of proteins and can potentially impact on structure and function of redox-sensitive targets [1] The protein S-glutathionylation is endorsed in conditions of oxidative stress and reversed when a reducing environment is restored so that the GSH moiety may be removed (deglutathionylation) [1].

S-glutathionylation takes part to the regulation of multiple cellular processes during stress, either preventing the disruption of protein function, as in the case of oxidative damage of mitochondrial respiratory complexes, or directly regulating protein activity [1]. S-glutathionylation is implicated in the development and progression of different diseases, such as cancer, neurodegenerative disorders, lung diseases, inflammatory diseases and diabetes [1]. S-glutathionylation also contributes to the genesis of cardiovascular disorders, such as atherosclerosis, hypertension and cardiac diseases [1]. S-glutathionylation directly targets sarcomeric proteins in the heart during stress thereby affecting cardiac function (Fig. 1). Previous work demonstrated that S-glutathionylation of titin affects the stability of the molecule and cardiomyocyte elasticity [2]. Similarly, S-glutathionylation of contractile proteins, such as α-actin, reduces their contractile force [1]. Myosin Binding Protein-C (MyBP-C) undergoes S-glutathionylation in response to high fat diet-induced glucose intolerance leading to the development of diastolic dysfunction [3]. These effects are reversed by mitochondrial antioxidants. Cardiac MyBP-C is also S-glutathionylated in response to high blood pressure and ranolazine treatment was found to reduce hypertension-induced MyBP-C S-glutathionylation and diastolic dysfunction [4]. Finally MyBP-C S-glutathionylation was also linked to diastolic dysfunction in a model of hypertrophic cardiomyopathy [5].

The article by Chakouri et al. extends our knowledge regarding the effects of oxidative stress and S-glutathionylation in the heart in response to physical exercise [6]. A physiological increase in ROS production was observed in the hearts of rats subjected to low intensity exercise, which was associated with an improved ventricular performance. On the other hand, high intensity exercise induced an exaggerated ROS accumulation with a decline in systolic and diastolic function. Post-translational modifications of sarcomeric proteins also differed depending on the intensity and duration of the exercise training. Moderate exercise induced S-glutathionylation of cMyBP-C and PKA-dependent phosphorylation of cMyBP-C and TnI. Conversely, prolonged exercise still caused cMyBP-C S-glutathionylation, which was, however, associated with reduced cMyBP-C and TnI phosphorylation and increased myofilament calcium sensitivity in this condition, despite a preservation of PKA activity. Isoproterenol administration mimicked the effects of training on ROS production and cMyBP-C S-glutathionylation suggesting an involvement of β-adrenergic signaling activation in these mechanisms. Importantly, the administration of BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea), a glutathione reductase inhibitor, increased cMyBP-C S-glutathionylation, decreased cMyBP-C and TnI phosphorylation and induced cardiac dysfunction in ex vivo experiments. These results may suggest that cMyBP-C S-glutathionylation directly mediates the detrimental effects of high intensity training on cardiac function independently of ROS production, since BCNU treatment did not induce ROS accumulation. However, since both moderate and strenuous exercise training induced cMyBP-C S-glutathionylation, other mechanisms may also underlie the detrimental cardiac effects of high intensity training. The exaggerated

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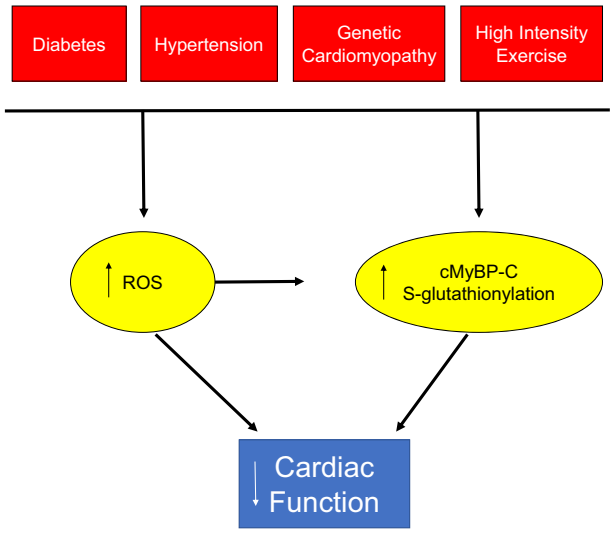

Fig. 1. Stress-induced oxidative stress and S-glutathionylation affect cardiac function. Schema summarizing the effects of different cardiac stresses on ROS production and cMyBP-C S-glutathionylation.

ROS accumulation definitively plays an important role, since the administration of *n*-acetylcysteine (NAC) reversed cardiac dysfunction and S-glutathionylation in rats subjected to an exhaustive exercise protocol. S-glutathionylation of additional protein targets may also be involved in the detrimental effects of exhaustive exercise training. In this regard, previous work demonstrated that S-glutathionylation of endothelial nitric oxide synthase (eNOS) and Na(+)-K(+) ATPase beta (1) leads to eNOS uncoupling and Na(+)-K(+) pump inhibition, respectively, which may contribute to the development of cardiac dysfunction [1].

Some aspects of the paper by Chakouri et al. [6] remain to be clarified. First of all, the molecular mechanisms through which physical exercise induces ROS accumulation need to be better clarified, also testing whether different exercise intensities regulate different redox processes. In this regard, the recognized molecular sources of contraction-induced ROS production in skeletal muscles include mitochondria, NADPH oxidase, PLA 2-dependent processes, and xanthine oxidase [7].

In addition, it will also be important to elucidate whether ROS production induced by low intensity exercise mediates adaptive mechanisms in the heart. It was previously demonstrated that a small increase in ROS production results in an increase in contraction force development, while high ROS concentration decreases it in skeletal muscles [7]. Exercise attenuates cardiac remodeling, reduces ischemic injury and improves cardiac metabolism in animal models [8,9]. Autophagy activation by exercise was found to be implicated in these cardiac beneficial effects [8]. It will be interesting to evaluate whether a physiological ROS production contributes to the beneficial cardiac effects of exercise. Of note, physiological ROS are important activators of autophagy.

Finally, previous evidence demonstrated that physical exercise induces ROS accumulation in human subjects, depending on the intensity of the training [7]. Among athletes, those practicing extreme endurance exercise training may develop signs of myocardial fibrosis overtime, suggesting myocardial damage [10]. It will be interesting to test whether the administration of antioxidants or S-glutathionylation inhibitors in these subjects may be beneficial to improve cardiac performance and reduce myocardial damage. Antioxidant nutraceutical compounds, such as flavonoids, may be highly suggested for these purposes.

Conflicts of interest

None.

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