Commentary

Molecular evidence that exercise training has beneficial effects on cardiac performance

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Numerous epidemiological and observational studies demonstrate that there is an inverse relationship between physical activity and risk of cardiovascular disease (1). Recently a few randomized controlled trials revealed that exercise training is not only effective as primary prevention, but also in the secondary prevention and thus can be viewed as a "medication" that should be taken on a regular basis by a patient with cardiovascular disease. Exercise in Left Ventricular Dysfunction (ELVD) trial in a small group of 77 patients with <40% ejection fraction after a first Q-wave myocardial infarction showed that a 6-month exercise training program prevented deleterious LV remodeling (2). The Heart Failure: A Controlled Trial Investigating Outcomes of Exercise Training (HF-ACTION) trial, enrolling 2,331 outpatients with stable systolic heart failure demonstrated that exercise training was associated with an 11% reduction in combined all-cause death or hospitalization (P=0.03) (3). A meta-analysis of exercise training trials in patients with chronic heart failure, majority of whom had a history of myocardial infarction, revealed that exercise training significantly reduced deaths and hospital admissions (4). Thus exercise training is recommended as part of a comprehensive approach to the patient with stable chronic heart failure (1).

Presumable mechanisms of this beneficial effect of exercise in the post-myocardial infarction and chronic heart failure setting include: improvement of VO2max, reduction of neurohormonal imbalance, antiarrhythmic effects, resolution of ventilatory abnormalities, improvement of endothelial function, improved both systolic and diastolic myocardial performance through improvement of cardiomyocyte contraction-relaxation cycle.

Cardiomyocyte contractile function has been shown to be impaired in post-MI heart failure. Decreased amplitude of myocyte contraction as well as slower kinetics of contraction-relaxation cycle has been demonstrated in many experimental models of post-MI heart failure and in humans (5,6). Cardiomyocyte contractile function is strictly controlled by beat-to-beat transient increase of intracellular Ca^{2+} concentration (i.e., calcium transient). After electrical activation, rising of the membrane potential opens the voltage-gated sarcolemmal L-type Ca^{2+} channels. This results in influx of small amount of Ca^{2+} to the myocyte, which activates the calcium-dependent sarcoplasmic reticulum (SR) Ca^{2+} release channels [ryanodine receptors (RyRs)]. This process is commonly called calcium-induced calcium release. Rapid release of considerable amount of SR Ca^{2+} results in increase of intracellular Ca^{2+} concentration and promotes Ca^{2+} binding to troponin C, a contractile apparatus regulatory protein. The change of tropnin C conformation upon Ca^{2+} binding enables actin-myosin interaction and thus myocyte contraction. Relaxation is initiated by termination of the Ca^{2+} release from the SR and by rapid Ca^{2+} removal from the cytosol. Two main transporting proteins are involved in this process: SR Ca^{2+}-ATP-ase (SERCA) which uses ATP to pump calcium back into the SR and the Na^{+}/Ca^{2+} exchanger (NCX) which transports 1 Ca^{2+} ion out of the cell and 3 Na^{+} ions into the cell. SERCA accounts for approximately 80% of removal of systolic calcium in humans and even more (about 90%) in rodents Thus, the transporting function of SERCA is the main determinant of the rate of cardiomyocyte relaxation. Additionally the SERCA transporting ability determinates the SR Ca^{2+} content and thus amplitude of

Ca^{2+} transient and amplitude of myocyte contraction. The transporting function of SERCA depends on its expression, intrinsic activity of enzyme (ability to utilize ATP) and the phosphorylation level of phospholamban, endogenous SERCA inhibitor. Phospholamban is phosphorylated at Ser-16 and Thr-17 by adrenergic stimulation dependent kinase (PKA) and calmodulin and Ca^{2+} dependent kinase (CAMKII), respectively and increase of phosphorylation level relives SERCA inhibition (7).

In post-MI heart failure detrimental changes in Ca^{2+} handling have been described. Decreased SERCA transporting function has been demonstrated consistently, due to both decreases of SERCA expression as well as decreased transporting ability, mainly due to reduced level of phospholamban phosphorylation. Moreover, in many animal models and in humans increased NCX expression or/and function has also been described. These changes are additionally accompanied by an increased Ca^{2+} sensitivity of RyRs due to their hyperphosphorylation which results in Ca^{2+}-leak from the SR independently from Ca^{2+} influx through the L-type Ca^{2+} channels (diastolic Ca^{2+}-leak) (8,9).

Decreased SERCA expression accompanied by increased NCX function results in increased proportion of intracellular Ca^{2+} removed from the cytoplasm by NCX as compared with SERCA. This together with increased Ca^{2+}-leak results in decreased Ca^{2+} SR content, amplitude of Ca^{2+} transient and myocyte shortening as well as the decreased rate of Ca^{2+} transient decay and slower relaxation. Moreover, increased NCX contribution to the relaxation increased inward current (1 Ca^{2+} ion is exchanged with 3 Na^{+} ions) and may promote afterdepolarization, premature beets and increased susceptibility to ventricular arrhythmias. Indeed the post-MI animals as well as patients with ischemic heart failure die from progressive pump failure or sudden arrhythmic events (10).

Many elegant papers have shown that regular, intensive aerobic exercise training influences Ca^{2+} handling and thus myocyte contraction and relaxation process in cardiomyocytes from both healthy and post-MI hearts (11).

In healthy animals exercise training resulted in approximately 30% increase of transporting activity of SERCA measured in the intact SR membranes or permeabilized cardiomyocytes (12). It was due to increased SERCA expression at mRNA and protein level as well as increased phospholamban phosphorylation. Additionally in some studies increased level of NCX and increased sensitivity of contractile apparatus were observed. Consequently, amplitude of the cell shortening and the rate of relaxation were increased (13).

In post-MI heart failure, exercise training seems to be especially beneficial. The restoration of the normal amplitude and rates of contraction and relaxation has been observed. It was associated with normalization of the expression of SERCA and NCX proteins. It supports the cardiomyocyte function and decrease propensity to Ca^{2+}-dependent ventricular arrhythmias (14). There is growing body of evidence indicating that exercise training is able to restore of the proper expression of the protein involved in Ca^{2+} handling in filing hearts the mechanisms of this restoration is still poorly understood.

The discovery of microRNAs (miRNAs), abundant single-stranded small (roughly 22 nucleotide long) nonprotein-coding RNAs, has made important contribution to the better understanding of mechanisms that regulate of gene expression. MicroRNAs have been shown to be involved in most biological processes, both physiological and pathophysiological, including cardiovascular diseases. MicroRNAs are transcribed as individual or in clusters, often as part of longer transcripts, and are expressed in a tissue and cell-specific manner. The miRNA system is generally regarded as a negative regulator of specific mRNA targets. They can inhibit translation and/or promote mRNA degradation by sequence-specific base pairing (15).

Many well documented studies revealed that microRNAs were frequently downregulated in various types of cardiac diseases, including pathogenesis of MI (16). Because miRNAs are important in many cardiac pathologies, they may play a functional role in exercise-induced cardiac phenotypes.

Melo *et al*. in their work titled "*Exercise training restores the cardiac microRNA-1 and -214 levels regulating* Ca^{2+} *handling after myocardial infarction*", published in *BMC Cardiovascular Disorders* (17) demonstrated that myocardial infarction in the rat resulted in reduced expression of SERCA and increased expression of NCX. Expression of microRNA-214 that targets SERCA, was increased, white that of microRNA-1 that targets NCX, was reduced. Ten weeks of exercise training resulted in restoration of both microRNA levels and prevents changes of expression of both calcium transporters induced by myocardial infarction. These results suggest that changes in microRNA are responsible for restoration of SERCA and NCX expression, through this conclusion is only based on the above mentioned correlations.

This article provides new data on possible mechanisms behind effects of exercise training on cardiac performance

in infracted heart. microRNA-1 is cardiac specific miRNA and plays a role in heart hypertrophy, myocardial infarction, and arrhythmias, by promoting apoptosis. Recently, studies have revealed that miR-1 was frequently downregulated in various types of cardiac disease but when overexpressed, played a protective role against cardiac hypertrophy or heart failure by regulating several hypertrophy-associated genes, including transcription factors, receptor ligands, apoptosis regulators and ion channels (18). Overexpression of microRNA-1 and other miRs is implicated in regulation of G-PCR and calcium handling (19). Second miRNA investigated by authors, microRNA-214, improved LV remodeling and decreased apoptosis of myocardial cell and had a protective effect on heart function (20).

In summary, the study by Melo *et al*. highlights new potential mechanisms of beneficial effects of exercise on the post-MI heart, providing new areas for future research.

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Footnote

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Comment on: Melo SF, Barauna VG, Neves VJ, *et al*. Exercise training restores the cardiac microRNA-1 and -214 levels regulating Ca2+ handling after myocardial infarction. BMC Cardiovasc Disord 2015;15:166.

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