Physical training, particularly in the case of aerobic exercise, has been shown to produce several physiological changes, among which are increase in the maximal oxygen uptake and general physical fitness, improvement in the sensitivity of some visceral reflexes, and decrease in the sympathetic drive to the heart, accompanied by increase in the vagal tone (e.g., [1,2]).

The reported effects of exercise on the heart in the absence of cardiovascular affections include enhancement of contractility, acceleration of Ca2+ transient and/or contraction kinetics, reduction of the oxygen requirements at increasing workloads, ischemic protection, and induction of anti-oxidant enzymes and chaperones [2–7]. Depending on the exercise modality, intensity and duration, myocardial hypertrophy may ensue. However, this so-called physiological hypertrophy differs from the hypertrophic growth that usually develops in response to chronic arterial hypertension and myocardial infarction. The latter is usually accompanied by increased expression of cell stress biomarkers (e.g., atrial natriuretic peptide), fibrosis, relative capillary rarefaction and greater propensity to arrhythmias, which are not observed in the physiological type of hypertrophy [8–11]. Thus, although hypertrophic growth is an adaptive response of the heart to increased hemodynamic load, physiological hypertrophy and pathological hypertrophy are quite distinct regarding the signaling pathway, morphological pattern, molecular and functional alterations, and evolution, as compensated pathological hypertrophy may progress to heart failure [2,8,9]. Nevertheless, it should be noticed that cardiac dysfunction and some phenotypic changes commonly observed in pathological hypertrophy can be induced by very intense and/or prolonged physical activity [12].

Would these 2 types of cardiac remodeling be superimposable? In the current issue of *Journal of Molecular and Cellular Cardiology*, Carneiro-Júnior et al., in their article *The benefits of endurance training in cardiomyocyte function in hypertensive rats are reversed within four weeks of detraining* [13], contribute to shed light on this issue reporting the molecular and functional effects of low-intensity endurance training (running) on the heart of spontaneously hypertensive rats, in which development of hypertension is associated with heightened sympathetic activity [14]. In their study, the authors observed that training, although not effective at normalizing the blood pressure, was able to reverse the myocardial overexpression of stress markers, one of the hallmarks of the pathologically hypertrophied heart. Their results are in agreement with previous data that indicate that different modalities of endurance training can lead to morphological, molecular and functional conversion of the pathological to the physiological hypertrophy phenotype in this hypertension model [15,16]. It should be pointed out, however, that this has not always been the case: failure of chronic exercise at improving cardiac function and producing beneficial effects was reported for compensated and decompensated hypertrophy induced by aortic constriction [17].

Carneiro-Júnior et al. [13] also described increased amplitude and acceleration of the timecourse of electrically-evoked Ca2+ transients and contractions in myocytes from trained normotensive and hypertensive animals. These changes, which were correlated with heightened exercise capacity, are reported both in the absence or in the presence of cardiovascular affections [2,4].

While the increase in contraction amplitude could be partially explained by enhanced myofilament sensitivity to Ca2+ after training [2], changes in cell Ca2+ handling might significantly contribute to the improvement of the contractile activity. Most authors have observed that long-term exercise training increases the ventricular expression of the sarcoplasmic reticulum (SR) Ca2+ -ATPase (SERCA) and/or the ratio of SERCA and phospholamban, its endogenous negative regulator [2,4,13,15]. Such alterations should result in increased SERCA activity, which could explain the concurrently observed faster decline of Ca2+ transients, as SERCA is the main pathway for removal of cytosolic Ca2+ in mammalian myocardium [18].

From the physiological point of view, upregulation of SERCA expression and activity should permit adequate ventricular filling at higher heart rates, which are reached during exercise, thus allowing that cardiac output be compatible with the greater metabolic requirement of the tissues. This is possibly the reason why the rate of decline of the Ca2+ transients and SERCA protein levels have shown correlation with exercise capacity [13,19]. Additionally, augmented SERCA activity may result in increase in the SR Ca2+ content. This change might greatly impact the amount of Ca2+ released from the organelle and made available for the myofilaments, mostly because the fraction of the SR Ca2+ content that is released at systole (fractional SR Ca2+ release) is determined, in a positive and non-linear fashion, by the amount of Ca2+ stored in the SR [20,21]. Although the excitation–contraction coupling efficiency has not been examined by Carneiro-Júnior et al. [13], such a mechanism might explain the greater Ca2+ transients observed by them and other authors, considering that the SR is the source of most of the Ca2+ that activates contraction. It still remains to be established whether exercise training and its associated increase in myocardial SERCA expression lead to greater SR Ca2+ loading and fractional release. In the case of hypertension models, the amount of released Ca2+ or the fractional release was found to be enhanced during the early phases of compensated hypertrophy [22], whereas it tends to decrease in the chronic state and progression to heart failure [23,24].

In this respect, it is noteworthy that, under unphysiological conditions (e.g., arterial hypertension, myocardial infarction), SERCA activity and expression are usually decreased [25], in contrast to its consistent enhancement reported after exercise training. This divergence in the two kinds of hypertrophic remodeling might be at least
Ca²⁺ influx also is a key factor in excitation–contraction coupling. Even for unchanged SR Ca²⁺ load, the fractional SR Ca²⁺ release can be enhanced by increase in the trigger of the release process, namely, the L-type Ca²⁺ current [20]. How exercise affects this trigger is a controversial issue and requires better clarification, as either increase, decrease or no change in the peak density of this current has been reported after aerobic exercise training [11,28,29].

Another potential mechanism affecting excitation–contraction coupling is the direct regulation of the SR Ca²⁺ release channel (or ryanodine receptor, RyR). Little information is available on the effects of physical activity on RyR function and regulation. Sánchez et al. [5] described exercise-induced increase in myocardial NADPH oxidase activity, RyR S-glutathionylation and in the rate of Ca²⁺-induced Ca²⁺ release after exercise, which suggests involvement of RyR regulation by reactive oxygen species. This mechanism might mediate stretch-dependent regulation of SR Ca²⁺ release [27].

While available evidence points out that exercise training can lead to myocardial remodeling associated with stimulation of Ca²⁺ cycling, and enhanced contractility and exercise capacity, it also indicates that this remodeling depends on the persistence of its inducer, namely, the regular physical activity. Two weeks detraining are sufficient for attenuation of the ventricular hypertrophy, the enhanced aerobic capacity, and the changes in Ca²⁺ transients and contraction brought about by long-term (8–13 weeks) endurance training. After 4 weeks of exercise cessation, such changes are no longer apparent [2,13]. These observations indicate the remarkable plasticity of myocardial regulation and the reversible nature of this type of remodeling of the myocardium, which requires continuous recruitment of regulatory mechanisms for its maintenance.

The growing knowledge on the cardiac effects of exercise has revealed important aspects of the dynamic and complex nature of the regulation of the myocardium, at molecular and functional levels. At the same time, it has pointed out the clinical relevance and potential of regular, moderate physical activity as a valuable non-pharmacological alternative for prevention of cardiovascular dysfunctions, as well as for improvement of cardiac performance of the diseased myocardium.

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References
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