Review

Cardiovascular Adaptations Induced by Resistance Training in Animal Models

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Abstract

In the last 10 years the number of studies showing the benefits of resistance training (RT) to the cardiovascular system, have grown. In comparison to aerobic training, RT-induced favorable adaptations to the cardiovascular system have been ignored for many years, thus the mechanisms of the RT-induced cardiovascular adaptations are still uncovered. The lack of animal models with comparable protocols to the RT performed by humans hampers the knowledge. We have used squat-exercise model, which is widely used by many others laboratories. However, to a lesser extent, other models are also employed to investigate the cardiovascular adaptations. In the subsequent sections we will review the information regarding cardiac morphological adaptations, signaling pathway of the cardiac cell, cardiac function and the vascular adaptation induced by RT using this animal model developed by Tamaki et al. in 1992. Furthermore, we also describe cardiovascular findings observed using other animal models of RT.

Key words: resistance training; cardiovascular adaptation; animal model

Introduction

Resistance training (RT) was first described to induce skeletal muscle adaptations. Experimental models that try to mimic these adaptations in rats, use a model of chronic muscle stretching, compensatory overload and electric stimulation in unconscious animals. However, today it is surrounded by controversy if these models to induce skeletal muscle hypertrophy are similar to that promoted by RT in humans [1–3].

On the other hand, RT in conscious animals was created by some laboratories to improve its similarities to RT performed by bodybuilders. These models provide an excellent means to study both acute and chronic responses of RT in the muscles. However, these models still have the challenge of training the animals to voluntarily perform the traditional exercises performed by humans. In some

cases, the animals are given food as a reward [4] or movement is stimulated by an electrical shock in the tail or leg, but not directly in the muscle tissue as in the previous unconscious animal models [2].

Tamaki et al., [2] created a model that mimics squat-training (figure 1) performed by humans, for rats and today it is the most common model used by many laboratories. The model was initially developed to compare metabolic and morphological adaptations in skeletal muscles in response to aerobic training and RT. After this first publication by Tamaki et al., other groups also used the same model to study the influence of RT in bone mass [5,6], in the metabolic processes [7] and in the body composition [8]. In 2005 our group were the first to use the same apparatus to examine the cardiovascular system and after that the number of studies using this model have grown to

investigate the effects of the RT as non-pharmaco-logical therapy for the treatment or prevention of the many different cardiovascular diseases [8–10].

Our first step was to perform the direct measurement of blood pressure (BP) and heart rate by a cannula inserted into the carotid artery. The cannula was connected to a polyethylene tube, and this to an electromagnetic transducer which was connected to an amplifier. From this, suing software, beat by beat values of systolic and diastolic blood pressure were obtained. Figure 2 is an example of a series of exercise. We can clearly observe the 12 pressure peaks corresponding to 12 repetitions performed, similar to weight lifters, that is characterized by the intermittent increase in BP during RT. In this context, our group began to investigate the effects of RT on the cardiovascular system in rats.

Cardiac hypertrophy

Cardiac hypertrophy (CH) is a central feature in several scenarios of pathological and physiological remodeling [11,12]. It is well recognized, that intermittent increase in BP during RT leads to pressure overload to the left ventricle. This pressure overload stimulus increases cardiomyocyte cell width and left ventricular wall thickning. This CH features are observed in bodybuilders and named as physiological concentric CH [13]. On the other hand, pathological concentric CH is observed in heart subjected to different diseases such as hypertension or aortic stenosis, where there is a continuous pressure overload to the left ventricle. This type of CH is followed by diastolic and/or systolic dysfunction and an uneven increase in the thickness of the left ventricle posterior wall and interventricular septum

Figure 1: Apparatus used to perform resistance training. Adapted from Barauna et al, 2005 [17].

[14,15]. However, the physiological CH developed by high level strength athletes may present a macroscopic structure similar to pathological CH, which could be incorrectly interpreted as pathological [16]. Therefore, here we will show our, and other authors results using the Tamaki Model about the morphological and molecular mechanisms responsible for physiological CH [2].

The results from our study [17], in 2005 demonstrated CH in rats in response to RT. We observed 12% increase in the heats of trained rats which is similar to previous reported in human training for less than 3 months [18,19], but a smaller than described in other studies in humans engaged for more than 1 year in RT programs [13,20,21]. In another study, in 2007, Barauna et al., [22] found that the left ventricular mass assessed by echocardiography was 8%, 12%, and 16% larger in the RT group, than in the control group in the first, second and third month respectively. This CH showed a similar increase in the interventricular septum and in the free posterior wall mass. There was no reduction in the end-diastolic left ventricular internal diameter during the 3 months of the RT period, showing that this stimulus leads to concentric CH. In addition, our group also investigated the morphology of the cardiomyocyte isolated from the left ventricular after eight weeks of RT [23]. In this study we confirmed that RT resulted in an increase in both width and volume of left ventricular cardiomyocytes when compared to sedentary control animals. However, cell length was not affected by exercise sessions. Therefore, our data shows that RT model due to an increase in pressure overload in the heart during the exercise, induces concentric cardiac cells hypertrophy, which is in agreement with previous echocardiographic data from our group [22].

Cardiac hypertrophy signaling pathway

RT increases cardiac workload during the exercise sessions and thus it is an interesting *in vivo* model for studying physiological pressure overload on cardiac cells. It has become clear that external load is sensed by cardiac cells and converted into intracellular signals [14]. Among the possible mechanosensors one of the most studied is the angiotensin II type 1 receptor (AT1R). AT1R activates a wide spectrum of signaling responses which mediates BP control, thirst and sodium balance as well as diverse pathological actions in the heart, kidney, and other tissues [24]. It is well established that AT1R plays an important role
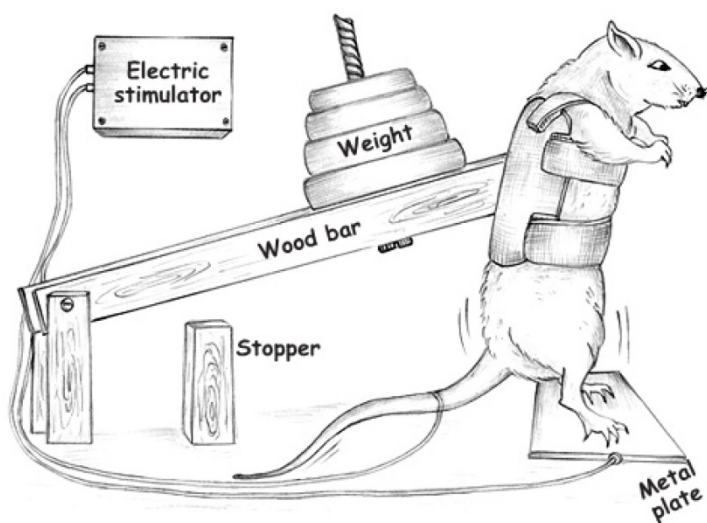
in the development of CH in pathological conditions such as in cardiovascular and renal diseases. However, in 2008, Barauna et al., [25] demonstrated that AT1R blockade prevented physiological CH induced by RT in rats suggesting that the AT1R and its intracellular signaling also plays a role in physiological CH induced by RT. Furthermore, no changes were observed in the angiotensin II levels or in its producing enzymes angiotensin-converting enzyme I (ACE) and renin activities, but increased expression of cardiac AT1R, suggesting AT1R activation by mechanical stretch as previous described by us and other groups [26,27].

In fact, Zou et al., [26] were the first to show the AT1R as a mechanical sensor in cardiomyocytes and to activate hypertrophic signaling pathways upon mechanical stimuli in the absence of angiotensin II. In agreement, Frank et al., [28] reported that AT1R activation by mechanical stretch is responsible for modulating genes involved in cardioprotection, which most likely occurs because of the AT1R ability to activate G-protein independent pathways. Cardiac-specific over-expression of mutated AT1R knocked out of G-protein signaling presented a higher degree of CH, but without fibrosis [29]. Zhai et al.,[29] also observed a reduction in apoptosis in the heart of these animals, corroborating the hypothesis that AT1R can activate pathways independent of G-protein, as in the case of exercise training, thus promoting physiological adaptations. In this regard, previous studies has suggested that AT1R may have beneficial effects, mainly thought β-arrestins, when it is biased activated to G-protein independent pathways [30]. Interestingly, in 2016, we highlighted that β-arrestin-2 gene expression is increased in rats subjected to RT for eight weeks [31].

Additionally, reports have shown that physiological CH induced by aerobic training is associated to tyrosine kinase receptors activation and downstream PI3K/Akt/mTOR signaling pathway [32]. In fact, studies have shown that insulin-like growth factor -1 (IGF-1) is involved in protein synthesis in physiological CH in both elite athletes [33] and trained rats [34]. However, Kim et al., [35] observed an unexpected increase in Akt phosphorylation even in trained IGF-1 receptor knockout animals also, suggesting that another pathway may be activated independent of the IGF-1 receptor. Interestingly, in 2011, we showed that a session of RT promoted increase in Akt phosphorylation 30 minutes after the RT session. This increased in Akt phosphorylation was also accompanied by an increase in phosphorylation of mTOR. However, these effects were blocked by blocking the AT1-R, suggesting activation of the AT1R-Akt-mTOR signaling pathway during a resistance exercise session as a potential mechanism for the CH [36].

Activation of MAPKs can also occur via G-protein pathway through adrenergic, endothelin-1, and AT1 receptors in animals subjected to pathological pressure overload (37). MAPKs are divided into 3 subfamilies on the basis of the terminal kinase involved in the pathway, namely: extracellular signal-regulated kinases (ERKs), P38, and c-Jun amino terminal kinase (JNKs). In an elegant study, Iemitsu et al.,[38] showed that cardiac ERK1/2 phosphorylation occurred 30 minutes after a session of aerobic exercise which decreased gradually with training adaptation (after 8 weeks of training). Similarly, Nakamura et al.,[39] showed that animals submitted to an exercise training protocol twice a week on a treadmill had increased ERK 1/2 phosphorylation, but with no signal of CH. In this sense, in 2011, we showed ERK1/2 phosphorylation via AT1-R after a session of RT, however, it is still unclear whether ERK 1/2 is a critical mediator of hypertrophic response during RT. Furthermore, we also observed that P38 activation increased after 5 and 30 minutes of a resistance exercise session which was not inhibited by AT1-R blockade, suggesting another upstream signaling pathway or the activation of this MAPK other than AT1-R [31]. Although MAPKs signaling pathway studies predominate in the field of cardiovascular disorders, little is known about their role or expression patterns in physiological conditions, especially RT-regulated MAPKs.

Cardiac Function

RT was shown by Barauna et al., [22] to induce physiological stimulus for concentric CH without cardiac dysfunction in rats. Consistently, our results are in agreement with results in humans showing no cardiac dysfunction in resistance trained
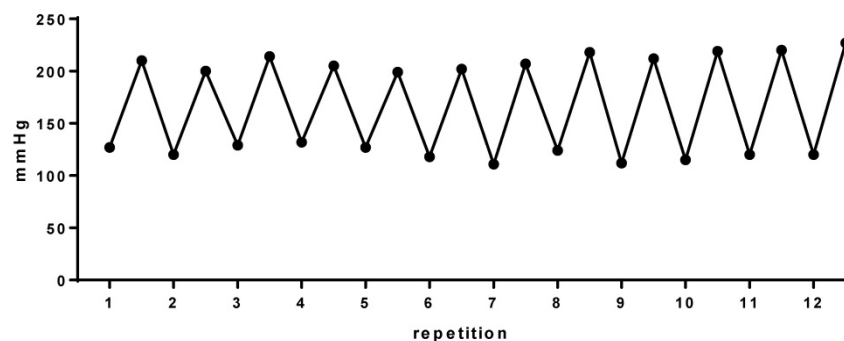
Figure 2: Blood pressure during 12 repetitions in a series of the resistance training in rats

individuals [18,20]. Later, in 2015, we observed that RT improved contraction and relaxation of isolated cardiomyocytes [13,23]. Although, not every possible mechanism had been tested, we showed at that time augmented expression of calcium regulatory proteins such as sarcoplasmic reticulum calcium ATPase-2a (Serca2a) in trained groups, which is responsible for 92% of Ca^{2+} reuptake [40,41]. We believe that this increased expression could at least partially explain the improved time to peak and time to half relaxation [13]. In this context, Pinter et al., [42] showed that in rats trained at 60% and 75% of 1RM there was an increase in the isometric force developed by the papillary muscles analyzed by the Langendorff technique. In this regard, the authors suggested that the improvement in cardiomyocyte contractility was due to increased myosin ATPase activity and enhanced Ca^{2+} influx after four weeks of RT. Furthermore, we showed that none of the pathological CH molecular markers such as atrial natriuretic peptide or α-MHC-to-β-MHC ratio were changed by RT in healthy rats [13,25].

On the other hand, in rats with pathological condition, such as in spontaneously hypertensive rats (SHR), Fernandes et al., [43] showed that acute RT increased isometric force of papillary muscles in isolated perfused hearts, as well as increased functional activity of the sarcoplasmic reticulum but with no change in Serca2a and phospholamban proteins expression. Additionaly, Alves et al., [44] showed that 12-week of RT in chronic heart failure rats were able to improve cardiac function and attenuate left ventricular collagen volume fraction. Although, Doustar et al., [45] showed that 4 weeks of RT did not preserve heart remodeling after ischemia–reperfusion injury, evidenced by no change in the infarct size and apoptosis rate, Soufi et al., [46], showed that 12 weeks of the RT reduced the infarct size and provides cardioprotection against ischemia–reperfusion injury. Recently, in 2017, we reported that RT prevented cardiac interstitial collagen deposition and attenuated diastolic dysfunction in rats subjected to a high salt diet independent of alterations in blood pressure [47] and that low intensity RT for 10 weeks in streptozotocin-diabetic rats induced an increase in systolic function and attenuation of cardiac autonomic neuropathy in diabetic rats [48]. Therefore, studies are still needed to understand the myocardial changes associated with RT in physiological and pathological situations.

Vascular adaptation

The effects of RT in the vascular system is still under investigation. A single session of aerobic exercise or RT reduces BP during the recovery period, which is called post-exercise hypotension (PEH). In normotensive subjects, the magnitude of the PEH has varied from −4/−2 to −14/4 mmHg of systolic/diastolic BP [49,50]. In hypertensive patients, it has been reported PEH from −12/−6 to −23/−14 mmHg, which is greater than the reduction observed in non-hypentensive subjects [51]. It is well established that exercise intensity (lower intensity promotes greater PEH [52,53] and volume (higher volume promotes greater PEH [54] are two determinants of PEH, however, endothelial function and autonomic mechanism of PEH is poorly understood after RT.

The PEH has been associated with improved nitric oxide (NO) synthesis, leading to a reduction in the peripheral vascular resistance [42,55] as well as reduction in the sympathetic nerve activity. In a study with SHR, both systolic and diastolic BP were decreased by -57 and -25 mmHg after 10 minutes of RT compared with pre-exercise values. PEH was abolished by L-arginine methyl ester (L-NAME) infusion, and the response to α-adrenergic stimulation in femoral artery was reduced due to buffering of NO after RT [55], suggesting PEH is mediated by increased NO production through eNOS activation [56]. In line with previous studies , Mota et al., [57], showed that acute RT promoted endothelium-dependent vasodilatation, eNOS phosphorylation and endothelial production of NO in the superior mesenteric artery of healthy rats, and the magnitude of these vascular endothelium adjustments were strongly related to the RT intensity. Furthermore, Fontes et al., [58] showed RT-induced enhanced insulin vasodilatation through both PI3K/eNOS and MAPK/ET-1 pathways evaluated by vascular reactivity of mesenteric artery.

A meta-analysis published by Cornelissen and Fagard [59] comprising 12 studies and 341 participants showed no significant reduction from -3.2 to -3.5 mmHg in resting mean BP in humans subjected to long-term RT. The same group of authors in another meta-analysis showed that both moderate-intensity dynamic RT and low-intensity isometric RT may reduce mean BP in subjects with optimal pressure and/or prehypertension [60]. However, the mechanism of such adaptations is still unknown.

In 2005, we observed reduction in the diastolic BP values in normotensive rats subjected to 8 weeks of RT at 70% of 1RM. After that, in 2008, Pinter et al., [42] showed a reduction in both systolic and diastolic BP in rats trained at 75% of 1RM but not when trained at 60% of 1RM. In a model of hypertension induced by L-NAME, Araujo et al., [9] showed that RT prevented the increase in mean and diastolic BP evaluated, and

maintained the arterial luminal-media ratio and total area of arteries' diameter. Recent findings suggested that the changes caused by RT are related to adjustments favoring augmented endothelial NO bioavailability and reduction of sympathetic vascular modulation [61]. In concert with the findings described above, Mota et al., [62] showed the effectiveness of RT to treat endothelial dysfunction and prevent an increase in arterial BP in type 1 diabetic rats. Karimian et al. [63] showed increased plasma angiogenic factors such as NO in diabetic rats after RT.

Other animal models of RT

Basically there are two different models to perform aerobic training in rats: running on a treadmill or wheel, and swimming [64-66]. In contrast, among different models of the RT, climb a vertical ladder [67] or jump in a water tank with the load apparatus attached to the tail [68], are RT models most commonly used in animals to study the cardiovascular system after the model by Tamaki et al. [2].

De Souza et al., [67], using the climbing a vertical ladder model, showed that RT promoted a 35% increase in CH, 17% in left ventricular thickness, 3% in left ventricular internal diameter and 27% in cross-sectional area of cardiomyocyte. Using the same model, Souza et al., [69] observed an increase in the aortic wall thickness, an increase elastic lamina and collagen fibers, and the thickness of collagen fibrils in trained rats. In this model, it was showed that RT reduced cardiac dysfunction in rats with diabetes [70] and in infarcted animals [71]. Furthermore , RT was associated to better metalloproteinases-2 activity in the left ventricle, systolic and diastolic BP in high-fat fed rats and to prevents obesity-induced cardiovas-

cular disorders, including an increase in mean arterial pressure, sympathetic modulation and impaired baroreflex sensitivity [72,73]. In addition, this model of RT has been shown to be effective in cardiac autonomic adaptations in healthy and SHR rats [74,75], to prevent chronic elevation in systolic BP in severe hypertension [76] and to improves hemodynamic status in diabetic ovariectomized rats [77].

On the other hand, fewer studies have used the models of jumping in the water to understand the cardiovascular adaptations. Junqueira et al., [68], showed increased left ventricular collagen density with no changes in proteins responsible for the calcium transport in the myocardial. McCulloch et al., [78], showed that the voluntary and forced jumping into water does not change the magnitude of the cardiovascular responses as such as immediate and substantial bradycardia [79]. However, using this model, RT did not reverse alterations in cardiac structure and function after pathological cardiac hypertrophy and injury induced by nandrolone administration [80].

Although some results were in agreement with findings with Tamaki Model, we cannot rule out the aerobic component, lack of similarity to the protocols performed by humans and also the poor standardization used in these animal models.

Conclusion

Based on our own findings and those reported by others, the RT model developed by Tamaki et al. [2] seems to be a good and appropriate model for studying cardiovascular adaptations. For the next step, we are studying the molecular mechanisms, mainly microRNAs, that mediate cardiac and vascular adaptations by RT.

Table 1. Cardiovascular adaptations induced by resistance training in animal models

Author	Target tissue	Duration	Intensity	Model	year
McCulloch et al.	Cardiac	5 weeks	No	Jumping into water	1990
Barauna et al.	Cardiac\Vascular	4 weeks	65-75% of 1RM	Squat-training	2005
Barauna et al.	Cardiac	For 1,2 and 3 months	65-75% of 1RM	Squat-training	2007
Barauna et al.	Cardiac	8 weeks	65-75% of 1RM	Squat-training	2008
Pinter et al.	Cardiac\Vascular	8 weeks	60% and 75% of 1RM	Squat-training	2008
Lizardo et al	Vascular	Acute	70% of 1RM	Squat-training	2008
Faria et al.	Vascular	Acute	50% of 1RM	Squat-training	2010
McCulloch et al.	Cardiac\vascular	5 weeks	No	Jumping into water	2010
Melo et al.	Cardiac	Acute	80% of 1RM	Squat-training	2011
Soufi et al.	Cardiac	8 weeks	70% of 1RM	Squat-training	2011
Yousef et al.	Cardiac\vascular	4 weeks	70% of 1RM	Squat-training	2011
Yousef et al.	Cardiac\vascular	4 weeks	70% of 1RM	Squat-training	2011
Tanno	Cardiac	6 weeks	50-70% body mass	Jumping into water	2011
Doustar et al.	Cardiac	4 weeks	70% of 1RM	Squat-training	2012
Ahmadiasl et al.	Cardiac	For 1 and 3 months	70% of 1RM	Squat-training	2012
De Deus et al.	Cardiac\vascular	10 weeks	75% body mass	Vertical ladder	2012
Araujo et al.	Vascular	4 weeks	50% of 1RM	Squat-training	2013
Mostarda et al.	Cardiac	10 weeks	40-50% of 1RM	Squat-training	2013

Author	Target tissue	Duration	Intensity	Model	year
Leite et al.	Cardiac\vascular	3 months	75% body mass	Vertical ladder	2013
Fontes et al.	Vascular	Acute	70% of 1RM	Squat-training	2014
Alves et al.	Cardiac\vascular	8 weeks	65-75% of 1RM	Squat-training	2014
Mota et al.	Vascular	8 weeks	50% of 1RM	Squat-training	2014
Grans et al.	Cardiac\vascular	3 months	75% body mass	Vertical ladder	2014
Sanches et al.	Cardiac\vascular	8 weeks	75% body mass	Vertical ladder	2014
De Souza	Cardiac	8 weeks	50% body mass	Vertical ladder	2014
Melo et al.	Cardiac	8 weeks	80% of 1RM	Squat-training	2015
Fernandes et al.	Vascular	Acute	50% of 1RM	Squat-training	2015
Mota et al.	Vascular	Acute	30,50 and 70% of 1RM	Squat-training	2015
Tharciano et al.	Vascular	Acute	40% of 1RM	Squat-training	2015
Ghiasi et al.	Cardiac	For 1 and 4 months	70% of 1RM	Squat-training	2015
Quinteiro et al.	Vascular	8 weeks	% of 1RM	Vertical ladder	2015
Lima et al.	Cardiac\vascular	4 weeks	75% body mass	Jumping into water	2015
Macedo et al.	Vascular	Acute	40% of 1RM	Squat-training	2016
Speretta et al.	Cardiac\vascular	10 weeks	75% body mass	Vertical ladder	2016
Neves et al.	Vascular	3 months	75% body mass	Vertical ladder	2016
Junqueira et al.	Cardiac	10 weeks	50% body mass	Jumping into water	2016
Speretta et al.	Cardiac\vascular	10 weeks	75% body mass	Vertical ladder	2016
Cunha et al.	Cardiac	5 weeks	50-70% body mass	Jumping into water	2016
Faria et al.	Vascular	Acute	50% of 1RM	Squat-training	2017
Hentschke et al.	Cardiac\vascular	8 weeks	65-75% of 1RM	Squat-training	2017
Souza et al.	Vascular	12 weeks	75% body mass	Vertical ladder	2017
Macedo et al.	Vascular	8 weeks	40% of 1RM	Squat-training	2017
Gomes et al.	Cardiac	8 weeks	75% body mass	Vertical ladder	2017
Rashidlamir et al.	Cardiac	8 weeks	30% of 1RM	Vertical ladder	2017
Barretti et al	Cardiac	8 weeks	80% of 1RM	Squat-training	2017

Acknowledgements

Competing Interests

The authors have declared that no competing interest exists.

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