BRAZILIAN JOURNAL
OF MEDICAL AND BIOLOGICAL RESEARCH
www.bjournal.com.br

ISSN 0100-879X
Volume 44 (11) 1070-1193 November 2011

BIOMEDICAL SCIENCES
AND
CLINICAL INVESTIGATION

Braz J Med Biol Res, November 2011, Volume 44(11) 1070-1079

doi: 10.1590/S0100-879X2011007500125

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The Brazilian Journal of Medical and Biological Research is partially financed by

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Brazilian Journal of Medical and Biological Research (2011) 44: 1070-1079
ISSN 0100-879X Review

Functional and morphological effects of resistance exercise on disuse-induced skeletal muscle atrophy

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Abstract

The reduction of skeletal muscle loss in pathological states, such as muscle disuse, has considerable effects in terms of rehabilitation and quality of life. Since there is no currently effective and safe treatment available for skeletal muscle atrophy, the search for new alternatives is necessary. Resistance exercise (RE) seems to be an important tool in the treatment of disuse-induced skeletal muscle atrophy by promoting positive functional (strength and power) and structural (hypertrophy and phenotypic changes) adaptive responses. Human and animal studies using different types of resistance exercise (flywheel, vascular occlusion, dynamic, isometric, and eccentric) have obtained results of great importance. However, since RE is a complex phenomenon, lack of strict control of its variables (volume, frequency, intensity, muscle action, rest intervals) limits the interpretation of the impact of the manipulation on skeletal muscle remodeling and function under disuse. The aim of this review is to critically describe the functional and morphological role of resistance exercise in disuse-induced skeletal muscle atrophy with emphasis on the principles of training.

Key words: Resistance exercise; Vascular occlusion; Eccentric exercise; Disuse; Atrophy

Introduction

The morphological and functional adaptations to resistance exercise (RE) have been well described, among them the positive responses of the neuromuscular system (neural adaptations) (1,2), muscle architecture (angle of pennation), biochemical composition (myosin heavy chain (MHC) isoform transition) (3,4), and the accumulation of myofibrillar proteins (5,6). These responses may occur according to the nature of the stimulus applied (i.e., the variables of the training program). In contrast to the positive response of muscle remodeling observed in some RE protocols, skeletal muscle atrophy is characterized by severe loss of muscle mass, specifically of contractile proteins (7). Generally, skeletal muscle atrophy can be defined as the unintentional loss of muscle mass due to catabolic states (8). Pathologically, there are some conditions that can induce it, such as cancer (8), sepsis (9), AIDS (10), diabetes (11), use of glucocorticoids (12), inactivity/disuse (13), chronic renal failure (14), and sarcopenia (15). In animals, experimental models of immobilization (16), use of corticosteroids or synthetic glucocorticoids (12), denervation (17), and even obesity (18) are used to mimic the catabolic states observed in humans in order to investigate the mechanisms behind the phenomenon.

Several studies using atrophic models have been performed with animals because better control of variables is possible. They have focused on molecular mechanisms responsible for modulating skeletal muscle protein metabolism (19). However, although the parameters investigated at the cellular level are relevant to the design of new interventions, little attention has been given to the principles of RE in atrophic conditions, i.e., studies have not evaluated the impact of training variable manipulation and/or control and application of different RE protocols on the functional and structural parameters of skeletal muscle in atrophic conditions. It is supposed that similar protocols of RE in different atrophic conditions may promote distinct

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Received April 12, 2011. Accepted September 9, 2011. Available online September 23, 2011. Published November 14, 2011.

adaptive responses since these catabolic states primarily differ in terms of cause (hereditary and non-hereditary) and cellular mechanisms responsible for the loss of muscle mass. Therefore, although there are several models and conditions able to induce muscle atrophy and RE may counteract muscle wasting and strength loss, the optimal characterization of RE in each of these conditions has not been completely elucidated.

Therefore, the purpose of this report is to review the effects of RE and its variables on the functional and structural parameters of non-hereditary and non-inflammatory skeletal muscle atrophic conditions characterized by muscle disuse such as inactivity (immobilization, bed rest and post-surgical cases) and lack of gravity. Worthy of note, the RE variables are approached separately in order to discuss the effectiveness of their characterization according to the model of RE. It is important to note that short periods of immobilization may result in significant strength loss but may not induce significant muscle atrophy (20). Thus, for this review we selected studies whose experimental design of muscle disuse resulted in significant skeletal muscle atrophy and loss of muscle function (strength). Considering also that immobilization protocols are more aggressive in terms of strength loss (21-23) than models of suspension or bed rest (24-26), the atrophic states were discussed separately and according to the model of training applied.

Why study the effect of resistance exercise on skeletal muscle atrophy?

One of the functional focuses of RE is to reduce muscle weakness and/or increase physical capacity (27). RE may also be considered a non-pharmacological treatment. For example, in elderly subjects muscle function and its ability to generate strength have been used as predictors of life expectancy (28). Recently, Spiering et al. (29) reported that the manipulation of RE variables promotes “fingerprints” in skeletal muscle at the cellular and molecular levels. Consequently, these “fingerprints” may be reflected on the functional and structural level and can be characterized, in general, as positive, negative or neutral adaptive responses. Thus, RE is a highly complex phenomenon and the manipulation of its variables can promote unique responses. The knowledge of such principles is extremely important for developing an effective training program.

Magnitude and functionality of different types of resistance exercise

Among the models of RE most commonly used in disuse atrophic states are flywheel (30-34), vascular occlusion (VO) (35), and conventional RE consisting of concentric/eccentric or isometric muscle actions (20,36,37). It is important to emphasize that the composition of these types of RE differs in terms of intensity and volume. For example, VO is a protocol characterized by low-moderate intensity, while flywheel and conventional RE usually consist of moderate-high intensity protocols. Muscle actions performed during flywheel RE are primarily eccentric and can be easily manipulated in conventional RE.

Some studies have used unilateral immobilization both in humans and animals with concurrent contralateral training. In this condition, it is essential to note that the cross-education phenomenon is present and may directly influence the functional and structural responses of the atrophied limb through neural adaptations (38-40). Therefore, unilateral immobilization is a condition that should be carefully evaluated. Furthermore, some of these studies have failed by using only internal control. Tables 1 and 2 summarize the main findings of published studies, highlighting the training models and their variables.

Flywheel resistance exercise

Flywheel RE is characterized by the lack of gravity. This type of RE has been applied in atrophic states induced by lack of gravity (i.e., during space missions), bed rest, and immobilization of the lower limbs. Tesch et al. (41), in a study of 4 individuals after 1 day of space mission, demonstrated that the isometric, concentric and eccentric strengths of the knee extensors were significantly reduced by approximately 10.2, 8.7, and 11.5%, respectively. Hence, the cross-sectional area (CSA) of the femoral quadriceps and gluteus femoral muscles was reduced by 8.0 and 8.5%, respectively. This same research group noted that individuals submitted to lower limb immobilization who performed RE (knee extension) in a flywheel for 5 weeks showed a significant gain of 7.7% in quadriceps volume and maintenance of basal strength (isometric strength at 90° and 120°) when compared with the untrained immobilized group (31). Rittweger et al. (33) chronically evaluated the role of flywheel RE in healthy young individuals submitted to bed rest with -6 degrees head-down for 90 days and observed that the trained group showed maintenance of 8.3% of thigh CSA when compared to the control group. Later, these investigators assessed the effect of this model of RE on the same experimental design in terms of vertical jump power 4, 7, 14, 90, and 180 days after 90 days of bed rest and observed that the delta of vertical jump amplitude and peak power after 4 days were -13 cm and -12.9 W/kg reduced in the control group and only -4.2 cm and -4 W/kg reduced in the trained group. Additionally, vertical jump amplitude and peak power were completely restored after 72 and 18 days, respectively, in the trained group while for the control group this occurred after 163 and 140 days (34). This model was further tested by Trappe et al. (32) who studied individuals submitted to 84 days of bed rest with -6 degrees head-down performing RE simultaneously. These investigators observed that the trained group showed preservation of size and function of the vastus lateralis muscle (isometric and isotonic strength), a 6% increase in MHC

IIa content and 19% of hybrid MHC I/IIa compared to 29% for the untrained group and did not show any decrease in fiber type I or IIa areas. Although the authors did not assess the phenotypic profile throughout the study, the increase of MHC I/IIa demonstrates that the muscle was in remodeling and adaptation processes at the time of evaluation and a further increase of MHC IIa content could be expected. Maintenance of power, peak power, and a 13% increase in the contractile activity of type IIa fibers were also observed. The studies of Trappe et al. (32) and Rittweger et al. (34) used the same model of muscle atrophy and tested a similar model of RE except for its variables, demonstrating the specificity of the mechanical stimulus.

In an experimental model, Fluckey et al. (42) developed a training apparatus for rats similar to the flywheel used in humans, with the detail that the animals trained in the hindlimb suspension position. This point is important because exposure to body overload could have masked the magnitude of the results. Hindlimb-suspended animals who trained for 4 weeks had higher absolute and relative soleus

Table 1. Effects of different forms of resistance exercise on functional and morphological responses of disuse-induced atrophied skeletal muscle.

Study	Resistance exercise	Results
HUMANS		
Akima et al. (30)	Dynamic	Increase of biceps femoris CSA and semitendinosus muscles
Ohta et al. (35)	Isometric with VO	Knee extensors
		60°/s concentric strength: maintenance of 26%
		180°/s concentric strength: maintenance of 19.4%
		60° isometric strength: maintenance of 1.9%
		Flexor muscles
		60°/s concentric strength: maintenance of 4.4%
		180°/s concentric strength: maintenance of 12.8%
		60° isometric strength: maintenance of 13.1%
Jones et al. (36)	Dynamic	Restoration of skeletal muscle mass
Tesch et al. (31)	Flywheel	Increase of 7.7% of quadriceps muscle volume
		Maintenance of 90° and 120° isometric strength
Trappe et al. (32)	Flywheel	Maintenance of size and function (isometric and isotonic strengths) of vastus lateralis muscle
		Increase of 6% of MHC IIa and MHC I/IIa isoforms
Rittweger et al. (33)	Flywheel	Maintenance of 8.3% of tight CSA
Rittweger et al. (34)	Flywheel	Maintenance of 8.8 cm and 8.9 W/kg in vertical jump amplitude and peak power after 4 days
		Restoration of amplitude and power of vertical jump after 72 and 18 days, respectively
Farthing et al. (20)	Isometric	Maintenance of isometric strength of an immobilized limb
Trappe et al. (37)	Dynamic	Reduction of 32% of peak power
		Reduction of 13% of calf volume
		Reduction of 15% of soleus muscle
		Reduction of 10% of gastrocnemius muscle
		Increase of soleus and gastrocnemius MHC IIa isoform
RATS		
Fluckey et al. (42)	Flywheel	Greater absolute and relative soleus muscle mass compared to an untrained group
Dupont-Versteegden et al. (43)	Flywheel	Increase of absolute and relative soleus and gastrocnemius muscles mass compared to an untrained group
Haddad et al. (52)	Dynamic	No significant results
Adams et al. (53)	Concentric/Eccentric/Isometric	Increase of absolute and relative gastrocnemius muscle mass compared to the contralateral limb
		Accumulation of myofibrillar proteins in trained limb

CSA = cross-sectional area; MHC = myosin heavy chain; VO = vascular occlusion.

Table 2. Description of training variables of different resistance exercise models for disuse-induced skeletal muscle atrophy.

Study	Condition	Duration	RE model	Contralateral training?	Volume (sets x repetitions)	Frequency	Intensity	Rest interval
HUMANS								
Akima et al. (30)	Bed rest	20 days	Dynamic	No	3 x 10 (Session 1) Until exhaustion (Session 2)	2 sessions/day (20 sessions)	90% 1RM (Session 1/day) 40% 1RM (Session 2/day)	1 min (between sets)
Ohta et al. (35)	Reconstruction of anterior cruciate ligament	16 weeks after surgery	Vascular occlusion (isometric)	Yes	2-3 x 20	6 times/week	Straight leg raising exercise Week 1: no load Weeks 2-4: 1 kg Weeks 5-8: 2 kg Half-squat exercise Weeks 5-6: no load Weeks 7-8: 4-6 kg Weeks 9-12: 8-10 kg Weeks 13-16: 12-14 kg	N/R
Jones et al. (36)	Immobilization	6 weeks of training after 2 weeks of immobilization	Dynamic	No	5 x 30	3 times/week	Maximal intensity	1 min (between sets)
Tesch et al. (31)	Immobilization	5 weeks	Flywheel	No	4 x 7	2-3 times/week	N/R	2 min (between sets)
Trappe et al. (32)	Bed rest	84 days	Flywheel	No	4 x 7	2-3 times/week	N/R	2 min (between sets)
Rittweger et al. (33)	Bed rest	90 days	Flywheel	No	4 x 14	Every 3 days beginning on the 5th day of rest	N/R	2 min (between sets) 5 min (between exercises)
Rittweger et al. (34)	Bed rest	90 days	Flywheel	No	4 x 14	Every 3 days beginning on the 5th day of rest	N/R	2 min (between sets) 5 min (between exercises)
Farthing et al. (20)	Immobilization	21 days	Isometric	Yes	3 x 8 progressively to 6 x 8	5 times/week	N/R	N/R
Trappe et al. (37)	Absence of gravity	6 months	Dynamic	No	3-6 x 12-20	3-6 times/week	N/R	N/R
RATS								
Fluckey et al. (42)	Hindlimb suspension	28 days	Flywheel	No	2 x 21	3 times/week	123.4 ± 7.2 g peak force for each repetition	N/R
Dupont-Versteegden et al. (43)	Hindlimb suspension	14 days	Flywheel	No	2 x 25	6 sessions	N/R	N/R
Haddad et al. (52)	Hindlimb suspension	6 days	Isometric	Yes	4 x 10	3 sessions	<25% of fatigue in each session	20 s (between contractions) 5 min (between sets)
Adams et al. (53)	Hindlimb suspension	5 days	Concentric/ eccentric/ isometric	Yes	Day 1: 3 x 10 Day 2: 4 x 10 Day 3: 4 x 10 Day 4: 5 x 10 Day 5: 5 x 10	5 sessions	<30% of fatigue in each session	27 s (between contractions)

1RM = one repetition maximum; N/R = not reported.

muscle weight when compared to the hindlimb-suspended animals without exercise. This same model was subsequently tested by Dupont-Versteegden et al. (43) who found that hindlimb-suspended rats, which trained for 2 weeks, increased their maximum strength during the experiment and presented higher absolute and relative gastrocnemius and soleus muscles weight than the untrained group.

Taken together, these studies demonstrate that acute and chronic flywheel RE is safe and effective both in animals and humans regarding the functional and structural adaptations of skeletal muscle. Independently of the composition of RE protocols, the mechanical stimuli provided by flywheel RE appear to be sufficient to attenuate muscle wasting and to promote functional and structural adaptations.

Resistance exercise with vascular occlusion

Since the study of Takarada et al. (44), much attention has been given to RE with VO. These investigators demonstrated that this type of RE, when performed chronically and by healthy subjects, can promote significant structural and functional modulation of skeletal muscle. It is already known that only VO may promote anti-atrophic effects and even hypertrophy. Takarada et al. (45) investigated the effects of VO without mechanical stimulation in patients who underwent reconstruction of the anterior cruciate ligament. The individuals were submitted to two sessions of occlusive stimuli per day on the proximal end of the thigh 3 to 14 days post-operation. Each session consisted of 5 repetitions of VO (mean arterial pressure: 238 mmHg) for 5 min and release of VO for 3 min. The group without the occlusive stimulus decreased CSA of extensor and flexor muscles by 20.7 and 11.3%, respectively, while the group that received VO decreased it only 9.4 and 2.6%. Recently, these data were confirmed by Kubota et al. (46) using the same protocol for ankle immobilization for 2 weeks.

Few studies have investigated the effects of RE with VO in atrophic models. The few reports available did not measure markers such as phenotypic transitions and primarily concerned individuals subjected to surgical procedures. Ohta et al. (35) investigated the effects of RE with or without moderate VO and consisting of isometric muscle actions in subjects subjected to reconstruction of the anterior cruciate ligament 16 weeks after operation. It was observed that the knee extension-trained group with VO showed a 10% decrease in concentric strength at 60°/s, an 8.3% decrease in concentric strength at 180°/s and an 8.7% decrease in isometric strength at 60° of extensor muscles. However, the trained group without VO presented a 36, 27.7, and 10.6% decrease in the respective measures. For the flexor muscles the reduction of strength at the above speeds was 15.6, 12.5, and 20.9% for the trained group with VO and 20, 25.3, and 34.0 for the trained group without VO. Regarding structural changes, although type I and II fibers were not significantly "hypertrophied", the trained group with VO showed a positive pre/post-operative relationship of extensor muscle CSA than the trained group without VO. It is important to emphasize that the authors reported some discomfort caused by VO in some patients and these were instructed to remove the occlusion for 15 min during training, which may have compromised the magnitude of the results. In another context, in a case report about an individual with inclusion body myositis, our group recently demonstrated that lower limb RE (knee extension) with VO for 12 weeks induced an increase of 11.6% in one repetition maximum strength tests (1RM), of 60% in mobility and of 4.7% in thigh CSA. Importantly, no side effects were observed (47).

Apparently, this model of RE is effective in preserving skeletal muscle mass and function under conditions of skeletal muscle disuse and can be considered a therapeutic non-pharmacological tool. As observed in flywheel RE, independently of the composition of RE protocols, the mechanical stimuli provided with VO training are also effective in skeletal muscle atrophy. Concerning the safety of VO training, Takarada et al. (44) postulated that VO may promote muscle damage and serious side effects such as thrombosis, and increase the levels of reactive oxygen species related to muscle proteolysis and apoptosis (48). However, these same authors did not find evidence of muscle damage or high levels of oxidative stress (49). In addition, Nakajima et al. (50) published the data obtained at 105 training centers in Japan where this model of RE is very popular for rehabilitation and even for the general population. In a total of 12,600 subjects who performed RE with VO in combination with different exercises (anaerobic and aerobic), the authors found low rates of side effects. VO has also been investigated and found to be effective in animal models under normal conditions induced by surgical procedures (51). Thus, VO can be further evaluated in different experimental models of skeletal muscle atrophy in combination with RE.

Conventional resistance exercise (dynamic, eccentric and/or isometric muscle actions)

Regarding practical applications, dynamic RE (consisting of concentric/eccentric muscle actions) or isometric RE would be more attractive for use in atrophic states because of control of training variables (especially if done using an isokinetic dynamometer), lower risk of hemodynamic disorders in comparison to training with VO, variability of exercises, and other variables.

In humans, Akima et al. (30) evaluated the effects of lower limb RE (leg press) in subjects undergoing 20 days of bed rest in the same experimental conditions as used by Rittweger et al. (33). They observed that the trained group showed significant preservation of femoral biceps and semitendinosus muscle CSA (corresponding to approximately 70% of the flexor muscles) compared to the untrained group. Jones et al. (36) investigated the role of isokinetic knee extension for 6 weeks after 2 weeks of unilateral lower limb immobilization. After the immobilization period, the lean mass of the individuals presented a reduction of about 5%, which was restored after 6 weeks of RE. Recently, Farthing et al. (20) assessed whether unilateral isometric RE on the upper dominant limb could mitigate the loss of strength in the immobilized limb (cross-training) for 3 weeks and observed maintenance of the basal isometric strength of the contralateral limb. Trappe et al. (37) conducted a study to assess structural and functional changes of skeletal muscle in individuals for 6 months of a space mission (lack of gravity). The training program consisted of moderate aerobic exercises (5 h/week) and RE that incorporated several exercises for the lower limbs. Functional and morphological tests were performed before and 6 months after the space mission and revealed a decline of 32% of peak power and a reduction of calf, soleus and gastrocnemius muscle volume of 13, 15, and 10%, respectively. However, there was a significant increase in MHC IIa content in the gastrocnemius muscle and the same trend for the soleus muscle. Although the results apparently show that RE was not effective in preserving the structural components of skeletal muscle, the study had no control (untrained) group. Thus, the magnitude of the effect of lack of gravity for 6 months could be extremely higher if individuals were not submitted to RE. With respect to phenotypic data, the hybrid MHC I/IIa content in soleus muscle was also increased, indicating that the subjects could still be in the phenotypic transition process.

In an animal model, Haddad et al. (52) investigated the role of isometric-induced muscle action in the prevention of gastrocnemius muscle atrophy in rats submitted to hindlimb suspension. The animals were suspended for 5 days with concomitant RE on days 1, 2, 4, and 5. The group without mechanical stimuli presented a 9% decrease of body mass, a 20 and 11% reduction of absolute and relative mass of the gastrocnemius muscle, respectively, and a 16% decrease of myofibrillar protein content. Although the trained group presented a reduction of only 8% in the gastrocnemius muscle mass the authors attributed this preservation, in part, to edema since the protein content of trained animals was 7% lower compared to the untrained group. Still, the content of myofibrillar proteins did not differ between groups. Based on these results, the authors concluded that RE with isometric-induced muscle action did not preserve muscle mass in an acute model of suspension. Later, these same authors improved this model of RE. In the same type of suspension, the animals were submitted to 5 sessions of RE combining unilateral isometric, concentric and eccentric isometric-induced muscle actions. In contrast to the first study, the trained limb presented similar absolute and relative gastrocnemius muscle weight and higher myofibrillar protein content than the contralateral limb (53). A critical point of the study of Adams et al. (53) was that muscle weight was not compared to a group that received no treatment. These two studies clearly demonstrate the role of RE variable manipulation in the functional and structural parameters of skeletal muscle in disuse-induced atrophy.

The main conclusion of the studies cited above is that mechanical contraction is a strong exogenous stimulus able to counteract the atrophic effects induced by muscle disuse. Both models of RE described appear to be effective in promoting significant structural and functional adaptations of skeletal muscle with different exercise protocols. However, it is important to emphasize that the control and manipulation of RE variables contribute significantly to skeletal muscle adaptations. In this context, it is supposed that the effectiveness of flywheel, VO and conventional RE could be optimized by means of different training regimes. It is difficult to compare the studies since they were conducted with different atrophic conditions, models and protocols of RE. Thus, the purpose of the next section is to describe the role of each RE variable in muscular adaptation and to describe how exercise protocols were conducted in the cited studies in order to elucidate the possible role of RE variables in counteracting disuse-induced muscle atrophy.

Resistance exercise variables

Volume and frequency

In general, it is known that training volume is inversely related to intensity and that it may modulate the nervous, metabolic, hormonal, and muscular systems (54). It is also known that it is still the current focus of research to quantify the ideal training volume since high and low volumes may be inefficient. In this context, training volume in disuse-induced skeletal muscle atrophy may or may not be determinant in promoting muscle adaptations as observed in normal conditions.

Regarding bed rest, Akima et al. (30) proposed a training volume of 3 sets of 10 repetitions performed in the morning followed by training until exhaustion in the afternoon (no details about the volume) in 20 sessions for 20 days (2 sessions/day). Trappe et al. (32) proposed a volume of 4 sets of 7 repetitions 2-3 times/week. The studies of Rittweger et al. (33,34) used a volume of 4 sets of 14 repetitions 3-4 times/week. Neither study described the training intensity, impairing the interpretation of the results. However, all showed positive morphological (32-33) and functional (32,34) results.

Ohta et al. (35), in a model of reconstruction of the anterior cruciate ligament, used a volume of 2-3 sets of 20 repetitions 6 times/week with low and progressive intensity. In unilateral immobilization, Jones et al. (36) used a training volume of 5 sets of 30 repetitions 3 times/week with maximum intensity. However, the study did not describe training intensity (% 1RM). Conversely, Tesch et al. (31) used a volume of 4 sets of 7 repetitions 2-3 times/week. Although Farthing et al. (20) worked with a progressive volume from 3 sets of 8 repetitions to 6 sets of 8 repetitions 5 times/week, the training protocol was applied to the contralateral limb. In terms of quantification of ideal volume, the lack of controlled parameters impairs the interpretation. The study of Munn et al. (40) showed that unilateral training conducted with a volume of 3 sets is more effective than a single set regarding strength gain by the disused limb. The main limitation of these studies is that they did not describe the intensity. However, since in normal conditions it is known that these variables are extremely important, extrapolation to disuse-induced skeletal muscle atrophy would be an interesting strategy.

The main consideration regarding training volume and frequency is how much muscle contraction is excessive or sufficient, i.e., if there is a minimum and maximum threshold and if it can vary according to the atrophic condition. To answer this question, studies with the same atrophic condition and RE model should compare the manipulation of frequency, sets and repetitions within an exercise protocol with the same intensity, and the rest interval between sets and repetitions. This evaluation should be performed in both healthy and atrophic conditions. Recently, our group demonstrated that a chronic low-frequency, low-volume, and high-intensity RE regime in energy-restricted animals promoted significant muscle remodeling (hypertrophy) (6). Since muscle disuse can be easily counteracted by body weight overload (13), it is supposed that a low-frequency and low-volume RE protocol may be effective in restoring muscle mass.

Muscle action

In humans, several studies assessing functional and structural adaptations of skeletal muscle under an RE stimulus have used an isokinetic dynamometer. Indeed, isokinetic RE is characterized by mechanical stimuli composed only of eccentric actions with the control of the muscle contraction velocity without losing tension. Among these studies, many conducted on a healthy population have shown that eccentric muscle actions performed at high velocity promote higher muscle functional (increase in isometric, concentric, and eccentric strengths) and structural (muscle hypertrophy) benefits than other muscle actions (55,56).

These results would be interesting regarding atrophic conditions since they could enhance the process of muscle regeneration and repair. Testing this hypothesis, Gerber et al. (57) evaluated the role of RE consisting of eccentric muscle actions or of dynamic actions in the muscle structure of individuals undergoing reconstruction of the anterior cruciate ligament. The subjects started the training program 3 weeks after surgery on an eccentric ergometer for 12 weeks. An increase of 23.1 and 24.2% in volume and CSA of the quadriceps muscle, respectively, was observed in the eccentric-trained group as opposed to 8.8 and 9.3% in the dynamically trained group. Similarly, the subjects who performed eccentric training had increases of 25.3 and 26.5% in volume and CSA, respectively, in the gluteus maximus muscle, as opposed to 9.8 and 9.6% of the dynamically trained group. The study clearly demonstrated the superiority of eccentric muscle action over conventional dynamic training even considering that the authors did not describe the speed of contraction.

The evidence that different muscle actions may exert significant modulation in atrophic conditions is also evident in experimental models. An example is the study of Adams et al. (53), which proposed an isometric RE apparatus for rats previously tested in hindlimb suspension-induced muscle atrophy by Haddad et al. (52), by including concentric and eccentric muscle actions with 1 s of duration for each one. Since the same experimental design was used for both studies and different results were observed, these studies clearly demonstrate that, as is the case for normal conditions, the manipulation of muscle actions, even acutely, promotes distinct muscle functional gains and structural adjustments in disuse-induced muscle atrophy. Indeed, the length of muscle tension was also higher in the second study, with the incorporation of concentric and eccentric muscle actions being assumed to play a significant role.

Although it is a practical limitation to apply only fast speed eccentric muscle actions within an RE protocol, the inclusion of these muscle actions in a rehabilitation program is suggested, but not as a single action. Thus, protocols composed only of concentric and/or isometric muscle actions could incorporate eccentric actions for better functional and structural adaptations (58). Therefore, as observed by Gerber et al. (57), eccentric RE in atrophic conditions may potentiate such responses. Munn et al. (40) demonstrated that dynamic high-velocity RE promotes better benefits than slow-speed training in muscle disuse. Additionally, there are no data assessing the role of RE with VO composed only of eccentric muscle actions with control of velocity contraction both in normal and atrophic conditions.

Intensity

It has been well described that RE performed at high intensity promotes positive and significant changes at the neuromuscular, structural and architectural levels (59). However, high-intensity training in atrophic conditions may not be tolerated. Holm et al. (59) compared in healthy adults the RE performed at 70% of 1RM (high intensity) and 15.5% of 1RM (low intensity) for 12 weeks with equal volume and frequency. Half the subjects performed high-intensity training in the dominant leg and low-intensity training in the contralateral leg, with the opposite being true for the rest of the sample. The authors observed that low-intensity training promoted a significant gain of 3% of quadriceps CSA and an increase of 19.2% of maximum strength. The hormonal responses were not altered with the training protocols, suggesting a hormone-independent muscle adaptation. If under non-atrophic conditions low-intensity RE can be effective, the question is: can low intensity RE promote positive structural and functional responses in atrophic conditions characterized by muscle disuse?

Regarding the studies that used flywheel RE, the obvious main limitation was the control of the intensity of eccentric muscle actions. In practice, acute and chronic human studies do not measure the intensity or even the functional parameters such as maximum strength (1RM).

Takarada et al. (44) showed that chronic low-intensity RE with VO promotes structural and functional benefits almost similar to high-intensity RE without VO. Ohta et al. (35) also reported positive results of chronic RE with VO at low intensity, which, although not directly described in the study, had mild-moderate load increments every 4 weeks of training. Complementing these data, Laurentino et al. (60) demonstrated that high-intensity RE with VO performed in normal conditions does not promote additional functional and structural effects compared to low intensity with VO. Such evidence is of extreme importance since high-intensity RE may not be tolerated in atrophic conditions. It is noteworthy that the training protocols of these studies consisted of dynamic and/or isometric muscle actions. Future studies should assess the effect of eccentric RE with VO at different intensities in the modulation of disuse-induced skeletal muscle atrophy.

Studies that assessed isometric or dynamic RE also did not describe RE intensity. Akima et al. (30) partially described the intensity of training performed during 20 days of bed rest (40% of 1RM to exhaustion on the second training session of the day). In studies concerning unilateral immobilization, Jones et al. (36) characterized 6 weeks of RE with maximum intensity. Although it is questionable whether such intensity should be applied to an immobilized limb, the training protocol began 2 weeks after immobilization, a fact that can be interpreted as a limitation since the return of the body overload during this period may have contributed to rehabilitation. Other human studies involving isometric (20) and dynamic (37) RE did not report the training intensity. In an experimental model, Haddad et al. (52) and Adams et al. (53) reported that the protocols used promoted less than 25 and 30% of peripheral fatigue in each session, respectively.

Body weight can be considered to be a low-intensity overload to a healthy lower limb. However, for an atrophied muscle group that underwent days or weeks of unloading or disuse, body weight overload may be considered to be a high-intensity stimulus. Therefore, since we proposed that a disused muscle group can be responsive to a low-frequency and low-volume exercise regime, we may assume that high-intensity could be incorporated into a conventional and well-tolerated RE protocol.

Rest interval

The rest interval between sets, repetitions and exercises is dependent on exercise intensity, training status, and metabolic pathway and may affect metabolic, hormonal and cardiovascular responses (54). According to Kraemer and Ratamess (54), short intervals for healthy subjects are ideal for muscle hypertrophy and longer intervals are needed for strength gain. Little is known about the manipulation of this variable in disuse-induced muscle atrophy and the choice of rest interval in the cited studies was apparently arbitrary or based on the "guideline" described above.

Regarding human studies, Akima et al. (30) found that leg RE with 1 min of rest between sets showed significant positive results. In the same atrophic condition, Rittweger et al. (33) used 2- and 5-min rest intervals between sets and exercises and observed maintenance of lower limb CSA in the untrained group. Later, the same authors also found recovery of muscle power with the same rest intervals (34). Trappe et al. (32) also used 2 min of rest interval between series and found maintenance of muscle function (peak force, velocity and contractile parameters of strength and power). In unilateral lower limb immobilization, Tesch et al. (31) used 2 min of rest between sets and observed increased quadriceps CSA. Jones et al. (36) observed that 1 min of rest between sets promoted restoration of skeletal muscle mass. The recent studies of Farthing et al. (20) and Trappe et al. (37) did not describe the rest intervals between sets and exercises. These results suggest that RE can promote rest interval-independent functional and structural changes. Since sedentary individuals who begin an RE program have strength and hypertrophy responses independent of the rest interval manipulation, it is supposed that in conditions characterized by disuse-induced skeletal muscle atrophy the principle may be similar.

Animal studies should be interpreted with care since they are performed in an apparatus where it is difficult to quantify exercise intensity. For example, Fluckey et al. (42) and Dupont-Versteegden et al. (43) tested flywheel RE where the measurement of intensity is limited and, although they observe positive results, they did not report the rest interval between sets. The studies of Haddad et al. (52) and Adams et al. (53) used sessions of RE with 20 s and 5 min of rest between contractions and sets, respectively, with relative intensity.

Conclusions and Perspectives

This review shows that in disuse-induced skeletal muscle atrophy, mechanical stimuli characterized by overload may be effective in the preservation or restoration of function and morphology of skeletal muscle. This response appears to occur with flywheel, VO, and conventional RE. However, the impact of different RE protocols (volume, intensity, frequency, and rest intervals) on atrophic conditions is unknown. The control and manipulation of RE variables are crucial in muscular responses. Thus, future studies assessing the role of RE in this and other atrophic conditions should evaluate the effects of manipulating RE variables in order to optimize functional and morphological responses. We suppose that such manipulation could promote distinct “fingerprints” in skeletal muscle that could optimize the therapeutic effects of RE.

Acknowledgments

H. Nicastro, N.E. Zanchi, and C.R. da Luz are supported by FAPESP (#2010/07062-3, #2010/52561-8, and #2011/04690-6, respectively).

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