Resistance Training with Vascular Occlusion in Inclusion Body Myositis: A Case Study

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AQ1 *[1]School of Physical Education and Sport, University of São Paulo, São Paulo, BRAZIL; [2]Division of Rheumatology, School of Medicine, University of São Paulo, São Paulo, BRAZIL; [3]Hospital Nove de Julho, São Paulo, BRAZIL; [4]Institute of Biomedical Sciences, University of São Paulo, São Paulo, BRAZIL; and [5]School of Arts, Sciences, and Humanities, University of São Paulo, São Paulo, BRAZIL*

ABSTRACT

GUALANO, B., M. NEVES JR, F. R. LIMA, A. L. PINTO, G. LAURENTINO, C. BORGES, L. BAPTISTA, G. G. ARTIOLI, M. S. AOKI, A. MORISCOT, A. H. LANCHA JR, E. BONFÁ, and C. UGRINOWITSCH. Resistance Training with Vascular Occlusion in Inclusion Body Myositis: A Case Study. *Med. Sci. Sports Exerc.*, Vol. 42, No. 2, pp. 00–00, 2010. Inclusion body myositis (IBM) is a rare idiopathic inflammatory myopathy that produces remarkable muscle weakness. Resistance training with vascular occlusion has been shown to improve muscle strength and cross-sectional area in other muscle wasting conditions. **Purpose**: We evaluated the efficacy of a moderate-intensity resistance training program combined with vascular occlusion by examining functional capacity, muscle morphology, and changes in the expression of genes related to muscle protein synthesis and proteolysis in a patient with IBM. **Methods**: A 65-yr-old man with IBM resistant to all proposed treatments underwent resistance training with vascular occlusion for 12 wk. Leg press one-repetition maximum; thigh cross-sectional area; balance, mobility, and muscle function; quality of life; and blood markers of inflammation and muscle damage were assessed at baseline and after the 12-wk program. The messenger RNA (mRNA) expression levels of mechanogrowth factor, mammalian target of rapamycin, atrogin-1, and muscle RING finger-1 were also quantified. **Results**: After the 12-wk training program, the patient's leg press one-repetition maximum, balance and mobility function, and thigh cross-sectional area increased 15.9%, 60%, and 4.7%, respectively. All Short Form-36 Health Survey Questionnaire subscales demonstrated improvements as well, varying from 18% to 600%. mRNA expression of mechanogrowth factor increased 3.97-fold, whereas that of atrogin-1 decreased 0.62-fold. Muscle RING finger-1 and mammalian target of rapamycin mRNA levels were only slightly altered, 1.18- and 1.28-fold, respectively. Importantly, the exercise did not induce disease flare. **Conclusions**: We describe a novel, and likely the first, nonpharmacological therapeutic tool that might be able to counteract the muscle atrophy and the declining strength that usually occur in IBM. **Key Words:** EXERCISE TRAINING, STRENGTH, IDIOPATIC INFLAMMATORY MYOPATHIES, MGF, ATROGIN-1

Inclusion body myositis (IBM) is a rare idiopathic inflammatory myopathy occurring in approximately 14.9 people per million, and it usually affects people at middle age and beyond (12). The pathogenesis of this sporadic acquired myopathy is still unknown, but some studies have revealed histologic evidence of inflammation in the affected skeletal muscle (12). The major feature of this disease is a remarkable muscle atrophy leading to proximal and distal weakness (13). Information available to guide evidence-based IBM treatment is lacking largely because of the very low prevalence of this disease. Moreover, clinical practice suggests that, unlike other inflammatory myopathies, most patients are not responsive to treatment with immunosuppressive or immunomodulatory drugs to counteract disease progression (4).

Until a few years ago, physicians have contraindicated physical exercise to patients with inflammatory myopathies because of the belief that it could increase inflammation in the affected muscles. This recommendation has changed after a few recent studies suggesting the safety of physical exercise for this population (4). Therefore, low-intensity physical training has been encouraged for patients with stable disease to help improve muscle function. However, low-intensity exercise does not seem effective in increasing

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muscle hypertrophy and strength. Exercise intensities within 70%–85% of one-repetition maximum (1RM) or 6RM–12RM are required to achieve these goals (7). Because high-intensity exercises may enhance the inflammatory response, the ideal type of exercise intervention for IBM patients should increase muscle strength and cross-sectional area while minimizing exercise intensity.

In this regard, Takarada et al. (17) observed that restricting muscle blood flow using tourniquet cuffs during moderate-intensity resistance training produces greater benefits to muscle cross-sectional area than high-intensity training. These findings have been demonstrated in athletes, the frail elderly, and in patients undergoing rehabilitation after surgery (18). The clinical application of this intervention may be of particular interest to IBM patients because conventional resistance training seems ineffective in counteracting muscle wasting (16,18).

The current case study describes the efficacy of a 12-wk moderate-intensity resistance training program combined with vascular occlusion in a patient with IBM. The goal was to determine whether this method of training could improve the functional capacity, alter the muscle morphology, and change the expression of genes related to muscle protein synthesis and degradation.

CASE STUDY

A 65-yr-old man (weight = 85 kg, height = 180 cm, $\dot{V}O_{2peak}$ = 10 mL·kg^{-1}·min^{-1} [assessed by $\dot{V}O_{2max}$ ramp test on cycloergometer]) presented 8 yr of symmetric proximal (i.e., quadriceps) and distal (i.e., finger flexor) muscle weakness with insidious onset and slow progression. Muscle atrophy was noted in the upper and lower limbs, especially in the quadriceps. Recurrent episodes of falls were reported without symptoms of myalgia or muscle tenderness. Muscle enzymes were never elevated, creatine kinase (CK) ranged from 167 to 267 U·L^{-1} (reference range = 39–308 U·L^{-1}), and aldolase ranged from 4.3 to 6.6 U·L^{-1} (reference range < 7.6 U·L^{-1}). Electroneuromyography revealed a myopathic pattern with irritability at rest (fibrillation potentials, complex repetitive discharges, positive sharp waves) and short-duration, low-amplitude, and polyphasic potentials on contraction. The diagnosis of IBM was then confirmed by the presence of intracellular lined (rimmed) vacuoles and endomysial inflammatory infiltrate with invasion of nonnecrotic fibers in a muscle biopsy. Toxic causes of myopathies associated with vacuoles were excluded (alcohol, chloroquine, colchicine, glycyrrhizin, zidovudine).

He was treated for 4 yr with prednisone (up to 60 mg·d^{-1}) and methotrexate (up to 20 mg·wk^{-1}) without a significant clinical response. After a minor clinical stabilization, methotrexate was discontinued, and prednisone was lowered to 2.5 mg·d^{-1}. The patient was also using acetylsalicylic acid, enalapril, glimepiride, insulin, metformin, pioglitazone, and replaglidine indicated for hypertension, diabetes, and psoriasis.

In addition to the pharmacological treatment, the patient had been in a physical therapy program for 1 yr including moderate-intensity strength exercises (i.e., 3 × 15RM for lower and upper limbs) before the vascular occlusion training started. Despite his adherence to the rehabilitation program, he reported a progressive decline on lower extremity strength and an inability to walk without a cane. These observations were further confirmed by his previous physical therapist who reported decrements in thigh circumference and lower limb strength (assessed by leg press 1 RM) of 7% and 5%, respectively. Moderate-intensity resistance training with vascular occlusion program was then initiated because of the patient's unresponsiveness to conventional training. The exercise program was performed twice a week, and it consisted of 3 × 15RM (30 s between sets) leg press, knee extension, and squat exercises performed with vascular occlusion at 50% of total occlusion pressure.

We assessed 1RM leg press strength (3); thigh cross-sectional area (by computed tomography scan); balance, mobility, and muscle function (i.e., timed up-and-go [15] and timed-stands test [14]); quality of life (i.e., Short Form-36 (SF-36) Health Survey Questionnaire and Health Assessment Questionnaire); and blood markers of inflammation (i.e., erythrocytes sedimentation rate (ESR) and C-reactive protein) before the start of the study and after the 12-wk program. Enzymes related to muscle damage (i.e., CK, lactate dehydrogenase (LDH), and aldolase) were measured on a weekly basis 24 h after the last training session. Moreover, muscle samples from before and after the 12-wk trial were taken from the vastus lateralis of the subject's right leg using the percutaneous biopsy technique. Approximately 60 g of sample was obtained, but only approximately 20 g corresponded to muscle tissue, which only allowed for mRNA study. All biopsies were performed after a 10-h overnight fast, and the last meal was a standardized dinner. It is worth mentioning that the postintervention biopsy was executed approximately 24 h after the last training session to allow for identifying changes in mRNA expression baseline values (9,19). The mRNA expression levels of mechanogrowth factor (MGF), mammalian target of rapamycin (mTOR), atrogin-1, and muscle RING finger-1 (MuRF-1) were quantified using real-time polymerase chain reaction following standard procedures described elsewhere (1). After the 12-wk trial, the patient had voluntarily refrained from any physical activity for 10 wk, so we assessed the effects of short-term detraining on 1RM leg press strength, balance, mobility, and muscle function. Of note, the patient underwent three familiarization sessions before the actual baseline physical tests (i.e., 1RM leg press, timed up-and-go, and timed-stands tests), separated by at least 96 h. The investigators were blinded to the biochemical tests and molecular assays.

To determine the blood pressure (mm Hg) of vascular occlusion, a vascular Doppler (DV-600; Marted, São Paulo,

Brazil) probe was placed over the tibial artery of the patient's dominant leg. The subject was kept in a supine position while a customized blood pressure cuff (180 mm × 80 mm) was fixed on his right thigh and inflated until it interrupted the auscultatory pulse of the tibial artery (8). The training pressure was established as 50% of the vascular occlusion pressure (~65 mm Hg).

Thereafter, after a brief warm-up on a treadmill, the patient performed three exercises per session, including the unilateral leg extension, the leg press, and the half-squat. Two pressure cuffs were positioned near the inguinal fold region on both thighs and inflated to the training pressure. The patient performed three sets of 15 repetitions, with 30 s of rest between sets. The cuff's pressure was maintained during the whole session, including intervals. Light stretching exercises were performed after the resistance exercises. Training intensity was adjusted according to the gradual increase in strength so the patient would be able to perform no more than 15RM. All sessions were monitored by at least two investigators. This trial was approved by the local ethical committee (University of São Paulo, School of Medicine, General Hospital), and informed written consent was given by the patient.

After the trial, the patient showed improvement in leg press 1RM values (15.9%). In addition, balance and mobility function, as assessed by the timed up-and-go test, was enhanced (60%), and the thigh cross-sectional area was T1 increased (4.7%). These data are presented in Table 1. All the SF-36 subscales indicated the patient's progress. The specific changes were 150% for physical functioning, 7400% for role–physical, 57% for bodily pain, 18% for general health, 267% for vitality, 600% for social functioning, 200% for role–emotional, and 43% for the mental health scales. However, Health Assessment Questionnaire scores were not altered. There was no change in the timed-stands test after the training period. In addition, after 10 wk of detraining, there was no difference in the 1RM leg press (−0.5%) and only a minor impairment in balance and mobility function (−20%). The coefficients of variation for thigh cross-sectional area, 1RM leg press, timed-stands test, timed up-and-go test, ESR, C-reactive protein, CK, LDH, and aldolase were 2%, 2%, 0%, 0.9%, 1.3%, 2%, 2.2%, 1.9%, and 2.2%, respectively.

Serum CK, LDH, aldolase, ESR, and C-reactive protein remained within normal levels (CK = 267 $U \cdot L^{-1}$ and aldolase = 5.1 $U \cdot L^{-1}$). There was no report of excessive exhaustion, pain, osteoarticular injury, or muscle soreness. Arterial blood pressure was also stable throughout the exercise program. A significant increase (3.97-fold) in MGF mRNA expression was observed, although atrogin-1 mRNA expression was reduced (0.62-fold). In contrast, MuRF-1 and mTOR mRNA levels were only slightly altered, 1.18- and 1.28-fold, respectively.

TABLE 1. Effects of 12-wk resistance training with vascular occlusion on thigh cross-sectional area, 1RM leg press, and timed up-and-go test in a patient with IBM.

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	PRE	POST
Cross-sectional area (cm^2)	117	122.5
1RM leg press (kg)	37	44
Timed up-and-go (s)	16	10

DISCUSSION

This case study suggests that 12 wk of moderate-intensity resistance training combined with vascular occlusion may increase muscle strength, thigh cross-sectional area, balance, mobility, and quality of life for IBM patients. MGF up-regulation and atrogin-1 down-regulation could explain the improvements in muscle morphology and function because such a response may ultimately lead to increases in muscle mass and force.

Some anecdotal effects have been attributed to vascular occlusion training such as thrombosis and damage to blood vessels (17), but to the best of our knowledge, there are no reports of vascular complications in the literature. In addition, Wernbom et al. (18) reviewed 13 studies on occlusion training, with 2–16 wk of follow-up for a total of 116 subjects trained. Except for acute muscle pain, no adverse effects were reported. Recently, Nakajima et al. (11) published a survey on the safety of this training mode on the basis of reports from 105 fitness and rehabilitation centers in Japan. The most common adverse effects reported by the 12,600 participants were subcutaneous hemorrhage (incidence = 13.1%) and temporary numbness (incidence = 1.3%). More serious adverse effects were rare: venous thrombosis (0.055%), deterioration of ischemic heart disease (0.016%), cerebral infarction (0.008%), rhabdomyolysis (0.008%), and pulmonary embolism (0.008%). Supporting this record of safety, none of these complications was observed in the patient studied herein. Long-term trials with larger numbers of IBM patients are necessary to validate the safety of this intervention.

IBM is resistant to all proposed treatments, and as a consequence, the aggravation of the muscle atrophy seems to progressively decrease the functional capacity (4). In this context, it has been suggested that physical exercise could result in functional benefits to IBM patients, leading to improvements in their quality of life (16). However, the outcomes of a few previous reports involving exercise training have been somewhat disappointing. Spector et al. (16) examined the efficacy of a strength training program in five patients with IBM. The program consisted of three sets of 10–20 repetitions for lower and upper limb muscles, three times a week for 12 wk. An increase in strength was observed in five of the eight exercises tested. However, the most marked benefits were seen in the least weakened muscles. Furthermore, there was no change in muscle size, as estimated by repeated magnetic resonance imaging. Another important study determined the efficacy of a home-based exercise program in seven patients with IBM

(2). The results indicated no significant alterations in fatigue and isometric peak power. These two studies suggest a limited response to exercise in these patients.

Alternatively, this lack of relevant benefits may be related to the low intensity of the resistance training. In fact, loads between 6RM and 12RM (70%–85% of the 1RM) seem to be more efficient for muscle hypertrophy (7). In the clinical setting, however, it is often difficult and sometimes contraindicated to use such high loads (18). Hence, interventions focused on muscle hypertrophy without the use of heavy loads should be of special interest in some chronic diseases where these loads are not recommended. Our moderate-intensity training program seems to be a valuable therapeutic option to improve strength, muscle hypertrophy, and most importantly, muscle function. For instance, Mackey et al. (10) reported a 3.7% increase in the cross-sectional area of the quadriceps after 12 wk of high-intensity resistance training in a healthy elderly group. Our patient increased the cross-sectional area of his thigh by 4.7%, which is similar to the response of a healthy elderly person. Moreover, he was able to walk on the treadmill at 5 $km \cdot h^{-1}$, without a cane, and his falling episodes were greatly reduced after this training. Finally, the improvements in the SF-36 subscales should also be emphasized because IBM patients usually have a poor quality of life (1,14). Overall, such aforementioned benefits are of great clinical relevance because there is no established therapy to stop disease progression. It could be argued that the observed benefits were due to a synergistic effect between our training program and the increased daily physical activity levels because the subject was able to walk without a cane by the end of the training program. However, it is important to emphasize that his participation in previous strength training programs improved neither muscle performance nor spontaneous physical activity levels (i.e., functionality). Thus, the likelihood that our vascular occlusion training program produced most of the described improvements is very high. It is also interesting to note that even after a 10-wk detraining period, the patient completely retained the strength benefits and partially retained the mobility and balance benefits of the training program. To the best of our knowledge, this is the first report of an IBM patient maintaining the training adaptations after a period of physical inactivity.

To shed some light in the molecular mechanisms behind the observed adaptations, we assessed the expression of a few genes related to muscle protein synthesis and degradation. A very encouraging piece of evidence was the marked increase in *MGF* gene expression after training. Although mRNA gene expression is an indirect marker of the muscle anabolic/catabolic state, previous studies have shown that mechanical overload does promote large increases in *MGF* gene expression, which has been associated with muscle hypertrophy (1,5). Therefore, it is reasonable to speculate that the fourfold increase in *MGF* mRNA expression stimulated muscle protein synthesis, leading to muscle hypertrophy. Furthermore, the 40% decrease in atrogin-1 gene expression suggests a decline in muscle proteolysis, a desirable effect in IBM patients because they have marked muscle atrophy. *Atrogin-1* and *MuRF-1* genes encode E3 ligases, which are involved in protein breakdown mediated through the ubiquitin–proteasome system. In fact, these genes are reliable markers of muscle atrophy through activation of the ubiquitin–proteasome system (6). It is important to note that the 18% increase in *MuRF-1* did not follow the same pattern as *Atrogin-1* because these proteins are part of the same ubiquitin–proteasome system. Likewise, expression of mTOR, a protein downstream of MGF, was enhanced slightly after the intervention, although a more dramatic increase was observed for MGF. Further work should investigate the mechanism for these differences.

Although our case study does not allow comparing physiological and functional improvements between resistance training with vascular occlusion and conventional resistance training, our findings are very promising. To the best of our knowledge, this is the first report of positive changes in quality of life and muscle cross-sectional area in an IBM patient after a nonpharmacological treatment. As described previously, other studies that used conventional training protocols did not report such extensive improvements (16). In addition, the fact that our patient had been previously engaged in a conventional resistance training program (the numbers of sets, repetitions, and lower limb exercises were the same as those in the current trial) and reported decrements in muscle strength supports the role of our intervention. However, caution should be exercised interpreting our findings because case studies do not allow drawing causal conclusion and generalization of the results.

In conclusion, our case study describes a novel, and likely the first, nonpharmacological therapeutic tool able to counteract the muscle atrophy and decline of strength that usually occurs in patients with IBM under conventional treatment. Interestingly, we show that short-term moderate-intensity resistance training with vascular occlusion using pressure cuffs leads to improvements in muscle function and quality of life, without inducing disease flare. Increased expression of MGF and down-regulation of atrogin-1 may contribute to the underlying cellular changes that mediate muscular improvement. These promising findings deserve additional controlled studies with larger samples.

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Bruno Gualano and Manoel Neves Jr contributed equally to this article.

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