UNIVERSIDADE FEDERAL DE SÃO CARLOS
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
PROGRAMA DE PÓS-GRADUAÇÃO EM FISIOTERAPIA

ANÁLISE DA COMPLEXIDADE DO TORQUE DOS EXTENSORES DO JOELHO: EFEITO DO ENVELHECIMENTO, FRAGILIDADE E EXERCÍCIO FÍSICO

ELIE FIOGBE

São Carlos

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RESUMO

O processo de envelhecimento fisiológico envolve uma série de alterações no sistema neuromuscular levando à redução da massa e da força muscular. Consequentemente, as modificações na força muscular tem sido investigada em indivíduos idosos como uma ferramenta para detecção de síndromes geriátricas e declínio da capacidade funcional. Contudo, ao contrário da força muscular máxima, os índices do controle da força muscular permitem uma melhor compreensão do sistema neuromuscular, fornecendo informações sobre os mecanismos que governam a produção e manutenção de força, refletindoo controle sensoriomotor destes indivíduos. No entanto, vários aspectos permanecem incertos no estudo do controle da força muscular em idosos. Dessa forma, os efeitos do envelhecimento, da intensidade de contração muscular e do treinamento físico sobre a complexidade da força de grandes músculos posturais ainda permanecen desconhecidos. Investigar essas questões terá uma grande relevância clínica, permetindo uma melhor compreensão das alterações no sistema neuromuscular devido ao processo de envelhecimento,bem como as suas respostas a um programa de exercícios multicomponentes. Com o intuito de elucidar esses aspectos, esta tese foi planejada em 3 estudos. O **Estudo I** intitulado **“Complexity of knee extensor torque: effect of aging and contraction intensity”** teve como objetivo investigar os efeitos do envelhecimento e da intensidade da contração isométrica na complexidade do torque extensor do joelho. Os resultados mostraram que embora a complexidade do torque dos extensores do joelho seja reduzida em idosos, sua relação com a intensidade da contração é semelhante à dos jovens. O **Estudo II** intitulado **“Exercise training in older adults, what effects on muscle force control? A systematic review of randomized clinical trials”** visou determinar a magnitude dos efeitos de diferentes modalidades de treinamento físico sobre variáveis de controle de força muscular em idosos, através de uma revisão sistemática da literatura. Os resultados desse estudo mostraram que o treinamento físico tem um efeito benéfico sobre o controle da força muscular de idosos. O **Estudo III** intitulado **“Effectiveness of a multicomponent training on muscle force control in pre-frail older adults: a blinded randomized controlled trial”** teve como objetivo investigar a eficiência de um programa de treinamento multicomponente em melhorar a capacidade funcional e a complexidade do torque dos extensores do joelho em idosos pré-frágeis. Os resultados desse estudo demonstraram a eficácia do programa de exercícios multicomponentes em melhorar a complexidade do torque dos extensores do joelho e a velocidade da marcha em idosos pré-frágeis.

Palavras-chave: Fragilidade, envelhecimento, exercício, controle da força muscular, entropia, força muscular, capacidade funcional.

ABSTRACT

The process of physiological aging involves a series of alterations in the neuromuscular system leading to the reduction of mass and muscle force. Consequently, changes in muscle strength have been investigated in elderly individuals as a tool for detecting geriatric syndromes and declining functional capacity. Consequently, muscle force is routinely assessed in older adults as diagnostic criteria of some geriatric syndromes, and a tool for the investigation of functional capacity declines. However, unlike maximal muscle force, muscle force control indexes allow a better understanding of the neuromuscular system, providing information on the mechanisms governing force production and maintenance, reflecting the sensorimotor control of these individuals. However, several aspects remain uncertain in the study of muscle force control in the elderly. Thus, the effects of aging, muscle contraction intensity, and physical training on large postural muscles force complexity of remain unknown. Investigating these issues will have a great clinical relevance, allowing a better understanding of the age-related changes in the neuromuscular system and its responses to the multicomponent exercise program. In order to elucidate these aspects, this thesis was planned in 3 studies. The **Study 1** entitled **"Complexity of knee extensor torque: effect of aging and contraction intensity"** aimed to investigate the effects of aging and the intensity of isometric contractions on the complexity of knee extensor torque. The results showed that although the knee extensor torque complexity is reduced in the elderly, its relation with the intensity of the contraction is similar to that of the young subjects. **Study II** entitled **"Exercise training in older adults, what effects on muscle force control? A systematic review of randomized clinical trials"** aimed to determine the magnitude of the effects of different modalities of physical training on muscle force control variables in older adults, through a systematic review of the literature. The results of this study showed that physical training has a beneficial effect on older adults' muscle force control. **Study III** entitled **"Effectiveness of a multicomponent training on muscle force control in pre-frail older adults: a blinded randomized controlled trial"** aimed to investigate the effectiveness of a multicomponent training program in improving the functional capacity and the complexity of the torque of the patients. knee extensors in pre-frail elderly. The results of this study showed the effectiveness of the multi-component exercise program in improving knee extensor torque complexity and gait speed in pre-frail elderly.

Keywords: Frailty, aging, exercise, muscle force control, entropy, muscle strength, functional capacity.

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LISTA DE ABREVIATURAS

%	Porcentagem
°	Graus
1-RM	One repetition maximum
ACSM	American College of Sports Medicine
ApEn	Approximate entropy
BML	Beginning Movement Load
BP	Blood pressure
CApEn	Corrected approximate entropy
CSampEn	Corrected Sample Entropy
CV	Coefficient of variation
ES	Effect size
ET	Exercise training
F	Female
FFT	Fast Fourier transform
FRT	Functional + Resistance Training
FT	Functional Training
FTSS	Five times sit-to-stand test
GRADE	Grading of Recommendations, Assessment, Development and Evaluations
HI	High Intensity
HR	Heart rate
HRR	Heart rate reserve
Hz	Hertz
LI	Low Intensity
M	Male
m	Embedding dimension

MulTI	Multicomponent Training Intervention
MVC	Maximum Voluntary Contraction
N	Newton
n	Sample size
N.m	Newton by meter
NCApEn	Normalized corrected approximate entropy
NCSampEn	Normalized Corrected Sample Entropy
OG	Old group
p	Significance level
PEDro	Physiotherapy Evidence Database
PT	Peak torque
r	tolerance
RCT	Randomized Controlled Trial
RM	Repetition-Maximum
RT	Resistance Training
s	Second
SampEn	Sample Entropy
SD	Standard deviation
SIC	Submaximal isometric contractions
THR	Training heart rate
YG	young group

SUMÁRIO

CONTEXTUALIZAÇÃO

Nas últimas décadas, a população idosa vem aumentando rapidamente no mundo. Estima-se que essa população representará aproximadamente 22% da população mundial em 2050 (SCULLY, 2012). No Brasil, dados epidemiológicos relatam um aumento do número de idosos de 19 milhões em 2010 para 24 milhões em 2015, e existem estimativas de que essa população alcance o número de 73 milhões em 2060 ("INSTITUTO BRASILEIRO DE GEOGRAFIA E ESTATÍSTICA", 2018).

O processo de envelhecimento fisiológico envolve um declínio das propriedades funcionais no nível celular e orgânico bem como uma redução gradual das reservas fisiológicas (HOLLIDAY, 1995). As pessoas idosas são caracterizadas por um risco particularmente alto para desfechos negativos devido a doenças crônicas e síndromes geriátricas cada vez mais prevalentes. A síndrome da fragilidade é atualmente considerada como uma das síndromes geriátricas mais prevalentes. Essa síndrome é descrita como um estado clínico de vulnerabilidade ao estresse devido ao declínio da resiliência e de reservas fisiológicas relacionadas ao envelhecimento, e um progressivo declínio na capacidade de manutenção da homeostase (CLEGG *et al.*, 2013; FRIED *et al.*, 2001). A síndrome da fragilidade tem sido relacionada a maior risco de desfechos adversos como mortalidade, quedas, institucionalização, hospitalização e perda de independência (FRIED *et al.*, 2005).

O processo de envelhecimento fisiológico envolve uma série de alterações no sistema neuromuscular. Assim, o decréscimo no número de fibras musculares (VANDERVOORT, ANTHONY A, 2002) a alteração da distribuição do tipo de fibra muscular (LEXELL, 1995), redução da área de corte transversal (KENT-BRAUN; NG, 1999), aumento de tecido fibrótico (SUNDARESAN *et al.*, 2015), distúrbios na ativação de células satélites (PUTMAN *et al.*, 2001), infiltrados gordurosos (HAMRICK; MCGEE-LAWRENCE; FRECHETTE, 2016), mudança para fenótipos mais glicolíticos e fadigáveis, atrofia muscular contribuem para a perda de massa muscular esquelética característica dos indivíduos idosos. No entanto, tem sido demonstrado que além dessa perda de massa muscular, ocorre uma redução da força neuromuscular devido a alterações neurais como a alteração na modulação da condução cortical das fibras proprioespinhais (PIERROT-DESEILLIGNY, 2002), reduções na excitabilidade dos motoneurônios alfa (DEVRIES *et al.*, 1985; SCAGLIONI *et al.*, 2002; VANDERVOORT, A A; HAYES, 1989), deficiência na transmissão sináptica na junção neuromuscular (BALICE-GORDON, 1997) e deficiências no acoplamento excitação-contração (PLANT; LYNCH, 2002). Dessa forma, evidências mostraram uma redução da força muscular com o aumento da idade, notavelmente para os músculos extensores do joelho (CANDOW; CHILIBECK, 2005; KUBO *et al.*, 2003, 2007; OVEREND *et al.*, 1992).

A força muscular tem sido rotineiramente estudada na população idosa como critérios diagnósticos de algumas síndromes geriátricas, mas também como meio de investigação do declínio da capacidade funcional decorrente ao processo de envelhecimento. Assim, em idosos saudáveis ou cursando a síndrome da fragilidade, a redução na geração de força dos extensores do joelho tem sido associada à declínio da capacidade de realizar atividades da vida diária, como andar (KIM *et al.*, 2000) e levantar-se de uma cadeira (HUGHES; MYERS; SCHENKMAN, 1996). No entanto, apesar de sua acessibilidade, as medidas de força máxima muscular não permitem investigar os mecanismos neurofisiológicos envolvidos no declínio da capacidade em idosos saudáveis ou frágeis.

Vários mecanismos regulam a força muscular cuja produção e manutenção dependem da integridade desses componentes, bem como da qualidade da interação entre si (CLARK; MANINI, 2008; VAILLANCOURT, DAVID E.; NEWELL, 2003). Durante uma contração muscular voluntária, a força produzida está sempre sujeita a flutuações não intencionais, também chamadas de tremor fisiológico (HERBERT, 2012). A análise dessas flutuações durante tarefas padronizadas tornou-se um método cada vez mais utilizado de avaliação do controle da força muscular (ARJUNAN, S. P.; KUMAR; BASTOS, 2012; ARJUNAN, SRIDHAR P.; KUMAR, 2013).

Ao contrário da força muscular máxima, os índices do controle da força muscular permitem uma melhor compreensão do sistema neuromuscular, fornecendo informações sobre os mecanismos que governam a produção de força (SLIFKIN; NEWELL, 2000). Rotineiramente, estudos investigam o controle da força muscular através dos índices estatísticos (desvio padrão e coeficiente de variação) (CONTESSA; ADAM; DE LUCA, 2009). Valores mais altos significam maior variabilidade de força o que significa um controle deficiente da força muscular (VAILLANCOURT, D E; SLIFKIN; NEWELL, 2002).

Entretanto, como consequência das interações entre os componentes do sistema neuromuscular, a força muscular flutua segundo um padrão irregular, não linear e complexo cuja estrutura temporal não pode ser analisada através dos índices estatísticos clássicos (VAILLANCOURT, DAVID E.; NEWELL, 2003). Portanto, foi proposto analisar a complexidade das flutuações de força muscular utilizando métodos derivados de dinâmicas não lineares como a entropia amostral (SampEn) (RICHMAN; MOORMAN, 2000) e a entropia aproximada (ApEn) (PINCUS, S M, 1991). Altos valores desses índices significam maior complexidade da força sugerindo um melhor controle de força muscular. Isso implica uma melhor capacidade para adaptar rápida e precisamente a força muscular em resposta a quaisquer demandas internas ou externas (LODHA *et al.*, 2010). As medidas da complexidade fisiológica são geralmente realizadas a partir de métodos derivados de dinâmicas não lineares baseadas na teoria do caos e fractais matemáticos (GOLDBERGER, 1996) e são úteis para a identificação precoce e degeneração pré-clínica, bem como para avaliar efeitos de estratégias de reabilitação e de prevenção (LIPSITZ, 2004). Sua redução, devido ao envelhecimento ou doenças, implica em perda do controle do sistema (LIPSITZ; GOLDBERGER, 1992) e reduz as interações entre os componentes do sistema neuromuscular, que cada vez mais passam a operar de forma isolada (PINCUS, STEVEN M., 1994).

Lipsitz e Goldberger postularam que o envelhecimento é caracterizado por uma perda de complexidade fisiológica (LIPSITZ; GOLDBERGER, 1992). Desde então, essa hipótese tem sido aplicada aos sistemas de controle cardiorrespiratório (CHAVES *et al.*, 2008) e postural (VASSIMON-BARROSO *et al.*, 2017). Um levantamento bibliográfico mostrou que tal hipótese foi pouco estudada no sistema neuromuscular. Além disso, as investigações encontradas sobre o assunto restringiram a musculatura da mão e punho (STURMAN; VAILLANCOURT; CORCOS, 2005). Embora esses músculos sejam frequentemente utilizadas, o desempenho locomotor bipodal parece ser mais representativo da independência física na realização das atividades da vida diária (equilíbrio postural, marcha, mobilidade, etc.) (MORITZ *et al.*, 2005).

Vários programas de exercícios têm sido investigados para serem usados como estratégia terapêutica para melhorar controle da força muscular (BARRY; CARSON, 2004) em indivíduos idosos. No entanto, a eficiência dos programas de exercício físico no controle da força muscular permanece incerta, uma vez que as evidências encontradas relatam resultados contrastantes, dependendo das características dos estudos (isto é, estado clínico da população de estudo, músculos avaliados, configuração experimental, parâmetros de análise de dados e modalidades exercício físico) (HORTOBÁGYI *et al.*, 2001) (KOBAYASHI *et al.*, 2014; TRACY; ENOKA, 2006).

Por outro lado, evidências sugerem que o processo fisiopatológico da síndrome da fragilidade é dinâmico, de evolução progressiva e gradual, e caracterizado por frequentes transições entre os diferentes níveis (GILL *et al.*, 2006). No entanto, deve ser ressaltado que o processo fisiopatológico dessa síndrome teria maior potencial de reversibilidade nos seus estágios iniciais (RODRIGUEZ-MAÑAS; FRIED, 2015).

A prática regular de exercício físico tem sido sugerida como um componente essencial no tratamento de idosos cursando a síndrome da fragilidade com o intuito de reduzir os efeitos deletérios dessa síndrome (CRUZ-JENTOFT, 2013; VELLAS; CESTAC; MORLEY, 2012). Porém, ainda não existem diretrizes sobre as modalidades de treinamento físico mais adequadas para essa população. No entanto, de forma geral, os estudos encontrados demonstraram a natureza superior dos programas de exercícios multicomponentes (que incluem componentes de força, resistência, equilíbrio / marcha e flexibilidade) quando comparados a programas de exercícios de componente único (GINÉ-GARRIGA *et al.*, 2014; SERRA-PRAT *et al.*, 2017; VILLAREAL *et al.*, 2011). Entretanto, muito poucas investigações envolveram idosos em estágio inicial de fragilidade (DEDEYNE *et al.*, 2017).

Baseado nesse contexto, este trabalho foi planejado em 3 estudos. O **Estudo I** intitulado **"Complexity of knee extensor torque: effect of aging and contraction intensity"** teve como objetivo investigar os efeitos do envelhecimento e da intensidade da contração isométrica na complexidade do torque extensor do joelho.

O **Estudo I** demonstrou que, embora a complexidade do torque dos extensores do joelho seja reduzida em idosos, sua relação com a intensidade da contração é semelhante à dos jovens. Como acima ressaltado, os efeitos do treinamento físico sobre o controle motor de indivíduos idosos ainda permanecem incertos devido à grande variedade das características dos estudos realizados até agora. Para preencher essa lacuna, foi então elaborado o **Estudo II** intitulado **“Exercise training in older adults, what effects on muscle force control? A systematic review of randomized clinical trials”**. Esse estudo visou determinar a magnitude dos efeitos de diferentes modalidades de treinamento físico sobre variáveis de controle de força muscular em idosos, através de uma revisão sistemática da literatura.

Os resultados do **Estudo II** mostraram que ao avaliar a eficiência do treinamento físico sobre o controle da força muscular de idosos, os estudos avaliam unicamente os índices da variabilidade da força em indivíduos saudáveis submetidos a programas de treinamento de componente único. No entanto, i) a síndrome da fragilidade é atualmente reconhecida como uma das principais síndromes geriátricas e tem sido mostrado mais reversível nos seus estágios inicias, ii) essa síndrome tem sido relacionada com a redução da complexidade fisiológica, e iii) os programas de treinamento multicomponente apresentaram melhores resultados do que programas de exercícios de componente único. Assim foi identificada a necessidade de elaborar um ensaio clínico como o objetivo de determinar a eficiência de um programa de treinamento multicomponente em melhorar a capacidade funcional e o controle da força muscular (avaliado por índices da variabilidade e da complexidade do torque) em idosos pré-frágeis. Assim, foi desenvolvido o último estudo, **Estudo III** intitulado **“Effectiveness of a multicomponent training on muscle force control in pre-frail older adults: a blinded randomized controlled trial”**.

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ESTUDO I

(Versão em inglês apresentada nas normas da revista)

COMPLEXITY OF KNEE EXTENSOR TORQUE: EFFECT OF AGING AND CONTRACTION INTENSITY

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ABSTRACT:

Assessing the knee extensors torque complexity in old adults is relevant since these muscles are among the most involved in functional daily activities. This study aimed to investigate the effects of aging and isometric contraction intensity on knee extensor torque complexity. Eight young (24±2.8 years) and thirteen old adults (63±2.8 years) performed three maximal (MVC, duration = 10s) and submaximal isometric contractions (SIC, targeted at 15, 30 and 40% of MVC respectively) of knee extensors. Torque signals were sampled continuously and the metrics of variability and complexity were calculated basing on the SIC torque data. The coefficient of variation (CV) was used to quantify the torque variability. The torque complexity was determined by calculating the corrected approximate entropy (CApEn) and sample entropy (SampEn) and its normalized versions (NCApEn and NSampEn). Young subjects produced greater isometric torque than old adults and the CV was similar between both groups except at the highest force level (40%MVC) where young subjects value was higher. The major novel finding of this investigation was that, although the knee extensor torque complexity is reduced in old adults, its relationship with contraction intensity is similar to young subjects. This means that, despite the age-related decrease of the interactions between the components of the neuromuscular system, the organization of force control remains preserved in old adults, at least up to just below the force midrange.

Key Words: torque output, old adults, muscle strength, nonlinear dynamics.

INTRODUCTION

The production and maintenance of voluntary muscle contractions result from interactions between multiple mechanisms (i.e., feedback loops, motor unit recruitment, motor unit firing rates, and attentional control) (34). It is well established that aging leads to decreased muscle strength (2,9) due to changes in the neuromusculoskeletal system (4). Muscle strength remains the most investigated neuromuscular output in older adults because of its clinical relevance and its accessibility; however, the effects of aging on other neuromuscular outputs (e.g., force variability and complexity) are less well investigated. This is relevant since these variables would allow a broader comprehension of the neuromuscular system. For instance, force complexity provides information about the interactions between components of the neuromuscular system (i.e., motor cortical neurons, spinal motoneurons, muscle fibers, and muscle afferents) that regulate the production of muscle force (27).

Lipsitz and Goldberger postulated that aging is characterized by a loss of physiological complexity (16), and since then this hypothesis has been applied to the cardiorespiratory (21) and postural control (7) systems. Vaillancourt and Newell (2003) extended it to the neuromuscular system as they found that older adults produced less complex force output during a sustained finger abduction task than younger subjects (33). Optimal force complexity (e.g. in young healthy subjects) means the ability to rapidly and accurately adapt muscle force in response to any internal or external demands (33). Its reduction, due to aging or diseases, implies a loss of system control (17) and reduced interactions between the components of the neuromuscular system, which increasingly begin to operate in isolation (22).

Furthermore, Slifkin and Newell (2000) found that there is a relationship between torque complexity and contraction intensity, with maximum values of complexity observed at 30–40% of the isometric maximum voluntary contraction (MVC) (28). This relationship represents the organization of the operating mechanisms underlying the force control system. Its underlying mechanisms are not fully understood; however, they are thought to be related to two neuro-physiologically mediated mechanisms. At initial levels, force is mainly increased by increasing the number of active motor units; however, once all motor units are recruited, further force increases are achieved through increases in the firing rate of the recruited motor units (7). Both the former and latter neural mechanisms are available just below the MVC midrange, which gives the neuromuscular system the broadest possibility of adapting the force output to the force target (8) and hence the highest complexity. The relationship between torque complexity and force levels has been demonstrated in young subjects (n = 29; age, 19.86 ± 2.3 years) (28). Unfortunately, the only related investigation involving healthy older adults (n = 11; age, 67 ± 1.7 years) restricted the musculature to the hands and wrists (36). Although these body parts are frequently used, bipedal locomotor performance is likely more reflective of physical independence in performing activities of daily living (e.g., self-lifting, postural balance, gait, mobility, etc.) (5,20). Therefore, an examination of the larger muscles controlling these actions in older adults would be particularly relevant.

Studies evidenced that the number of motor unit decreases with advancing age (19) and the relative contribution of motor unit recruitment and firing rates in muscle force generation differs between larger postural and intrinsic hand muscles (1). Thus, when an old adult performs a knee extensors contraction, it would be expected that, i) as consequence of the reduced number of motor units, the most of the available motor units are already recruited at lower force levels than in young subjects, and accordingly, ii) increasing the firing rate of these recruited motor units would be necessary at lower force levels than in young subjects. Thereby, in older adults, both neural control strategies would be available at a region lower than in young subjects. In other words, in older adults, the highest knee extensors torque complexity would coincide with a force region below 30-40% of MVC. Therefore, this study aimed to investigate the interaction of aging and isometric contraction intensity on knee extensor torque complexity. We hypothesized that, as a function of force level, knee extensors torque complexity would follow a steeper slop in older adults, with maximum value observed at lower force levels than in young subjects.

METHODS

Experimental Approach to the Problem

To test the hypothesis, 21 volunteers were subdivided into two groups (young and older adults), and the steadiness of submaximal isometric knee extension across target forces (up to just below the force midrange) was assessed. Subjects were required to visit the laboratory on the day before the experiment to familiarize themselves with the procedures and equipment to be used. They were instructed to avoid caffeinated and alcoholic beverages and moderate-to-heavy exercise in the 24 h preceding the protocol. They were interviewed on the day of the experiment to confirm their health condition and the occurrence of a regular night sleep. All subjects were evaluated at the same time of day. The experiments were carried out in a climatically-controlled room at 22–23°C with relative air humidity of 50%–60%.

Subjects

A total of 21 healthy males volunteered to take part in this study. They were divided into a young group (YG) (n = 8 (mean ± SD): age, 24 ± 2.8 years (23 - 26 years); weight, 80.63 ± 14.77 kg; height, 179 ± 7 cm; body mass index, 25.14 ± 3.37 km/m^2; VO_{2max}, 29.63 ± 6.62 ml/min per kg; peak torque (PT) value, 222.85 ± 56.56 N.m) and an old group (OG) (n = 13 (mean ± SD): age, 63 ± 2.8 years (60 - 66 years); weight, 71.24 ± 5.06 kg; height, 168 ± 5 cm; body mass index, 25.15 ± 1.03 km.m^2; VO_{2max}, 27.08 ± 3.3 ml/min per kg; PT value, 177.45 ± 28.6 N.m). All subjects were deemed to be healthy based on their clinical and physical examination and on laboratory tests that included a standard electrocardiogram, a maximum exercise test conducted by a physician, a chest X-ray, a total blood count, urinalysis, and a clinical biochemical screening test (e.g., glucose, uric acid, creatinine, urea, total and fractionated cholesterol, and triglyceride levels). Subjects with hypertension, neurological injuries, and skeletal muscle diseases were excluded. The subjects were informed about the experimental procedures and signed a formal acceptance form approved by the institutional ethics committee of the Federal University of São Carlos.

Procedures

Isometric MVC

The MVC of the dominant leg knee extension was tested at 60° of knee flexion (full extension = 0°) using an isokinetic dynamometer (Biodex Multi-Joint System III, Biodex Medical System Inc., Shirley, NY, USA). The load cell was calibrated before each test by positioning and stabilizing the lever arm parallel to the floor and by hanging a known weight on the load cell. Subjects were positioned on the dynamometer chair (seat back angle = 90°)

and were stabilized by using pelvis, chest, and thigh straps. The rotational axis of the dynamometer was aligned with the lateral femoral epicondyle, and the resistance pad was distally positioned above the malleoli on the lower leg, still allowing full ankle dorsiflexion. The gravity correction factor, which is the additional torque produced by the leg segment and by the resistance pad weights, was determined at approximately 60° below the horizontal position when the subject was relaxed.

The subjects performed three MVCs (duration = 10 s) with a resting period of 10 min between each contraction. During the MVC, subjects were motivated with loud and consistent verbal encouragement and were instructed to pay attention to the visual feedback generated by the isokinetic dynamometer screen, to avoid contracting other muscles, and to keep breathing spontaneously. The highest of the three MVCs was used as the PT value.

Submaximal Isometric Contraction (SIC)

Subjects performed three single-repetition submaximal isometric contractions of the dominant-leg knee extensors at 15%, 30%, and 40% of the predetermined maximum isometric PT. The contractions were performed consecutively in a fixed order (i.e., 15, 30, and 40%) and were maintained for 30 s with a 10-min resting period between each contraction.

Data Acquisition and Analysis

Data were acquired from an isokinetic dynamometer (Biodex Multi-Joint System III, Biodex Medical System Inc.), which collected the torque output signal at a sampling rate of 100 Hz. All metrics of variability and complexity were calculated using the SIC data. To eliminate the transient effects of the initial isometric torque adjustments and early termination, the first 7 s and final 1 s of torque samples from each contraction were removed. The steadiest 3 s from the remaining torque samples were used for subsequent analysis.

The torque variability of each contraction was measured using the coefficient of variation (CV). The torque variability quantifies the ability to control muscle force during different standardized tasks (i.e., steady contractions) by evaluating the magnitude of fluctuations in torque output through within-subject standard deviation (SD) or using the CV. While the SD measures the absolute amount of variability, the CV measures the relative variability by normalizing the SD with the mean torque value. The CV is preferred in investigations of age-related changes in force or torque steadiness as, unlike SD, it addresses the age-related bias in muscle strength (3,32). The temporal structure of the torque fluctuations (i.e., the torque complexity) was examined using the corrected approximate entropy (CApEn), sample entropy (SampEn), and their normalized versions (NCApEn and NSampEn, respectively) (12,14,15). The input parameters for the calculation of CApEn and SampEn were an embedding dimension (m) of 2, a tolerance (r) of 0.2, and a sample size (n) of 300. All computed indices (i.e., CApEn and SampEn) were calculated using a strategy to correct the estimation bias arising from the small sample size. Normalization was carried out over all indices to reduce the dependence of complexity indices on the shape of the probability distribution. Normalization was carried out by dividing the index by the estimate of the Shannon entropy (17). Further details regarding the estimation and normalization procedures are described by Porta et al. (24–26).

Statistical Analyses

All data are presented as mean ± SD. A two-way analysis of variance with repeated measures was used to test the differences between groups and force levels for torque mean value, variability (CV), and complexity (CApEn, NCApEn, SampEn, and NSampEn). A linear regression was performed between each variable and SIC, and the regression parameters (slopes and intercepts) were compared between the YG and OG. The significance level was 5% and statistical analysis was performed in SigmaPlot 11.0 (Systat Software, San Jose, CA, USA).

RESULTS

The SIC, CV, and complexity indices are presented in Table 1. Figure 1 shows the linear regression of torque complexity versus SIC in the YG and OG. Table 2 presents the comparison of the regression parameters (slopes and intercepts) between the YG and OG.

Statistical analysis of the torque value revealed an effect of the force level but no group effect, and no significant group-by-force level interaction was observed. Table 2 shows that the slopes were similar while the intercepts of the YG were higher than those of the OG, therefore young subjects produced larger isometric torque than older adults.

Torque Variability

Statistical analysis of the CV revealed a significant group-by-force level interaction; however, there was no effect of force levels or group. At 40% MVC, the YG presented a higher CV than the OG ($P = 0.001$).

Torque Complexity: CApEn, NCApEn, SampEn, and NSampEn

Analysis of all complexity measures revealed main effects of both force levels and group, but no significant group-by-force level interaction. Therefore, the value of all complexity measures increased with force levels regardless of the group, and the torque complexity was higher in the YG compared to the OG. Figure 1 and Table 2 show that for all torque complexity measures, there were no differences in the slopes between the groups while the intercepts of the YG were larger than those of OG. The changes in all measures of the torque complexity as a function of the force levels were similar in both groups.

Table 1: Torque variability and complexity during the submaximal contractions in both groups

	YG			**OG**			**p Value**		
	15%	**30%**	**40%**	**15%**	**30%**	**40%**	**Group**	**SIC**	**Interaction**
Variable									
Torque (N.m)	33.11±8.16	64.43±15.33	84.65±25.56	26.54±4.31	54.11±9.75	69.41±10.24	0.105	<0.001*‡†	0.316
Variability									
Coefficient of variation (%)	1.52±0.43	1.41±0.48	2.09±0.76*†	1.36±0.42	1.36±0.43	1.24±0.36$^{\#}$	0.096	0.064	0.004
Complexity Indices									
CApEn	1.79±0.60	2.47±0.62	2.86±0.61	1.27±0.47	1.98±0.54	2.30±0.50	0.004	<0.001*‡	0.985
NCApEn	0.87±0.20	1.10±0.24	1.25±0.25	0.69±0.14	0.89±0.20	1.00±0.20	0.002	<0.001*‡	0.889
SampEn	0.94±0.28	1.34±0.30	1.57±0.28	0.71±0.23	1.04±0.27	1.18±0.19	0.002	<0.001*‡†	0.614
NSampEn	0.51±0.12	0.64±0.12	0.73±0.12	0.43±0.08	0.50±0.11	0.55±0.08	0.001	<0.001*‡†	0.265

YG: young group; OG: Old group; CApEn: corrected approximate entropy; NCApEn: normalized corrected approximate entropy; SampEn: sample entropy; NSampEn: normalized sample entropy; SIC: submaximal isometric contraction; *P<0.05: 40% MVC vs 15% MVC; ‡P<0.05: 30% MVC vs 15% MVC; † P<0.05: 40% MVC vs 30% MVC; #P<0.05: YG vs OG.

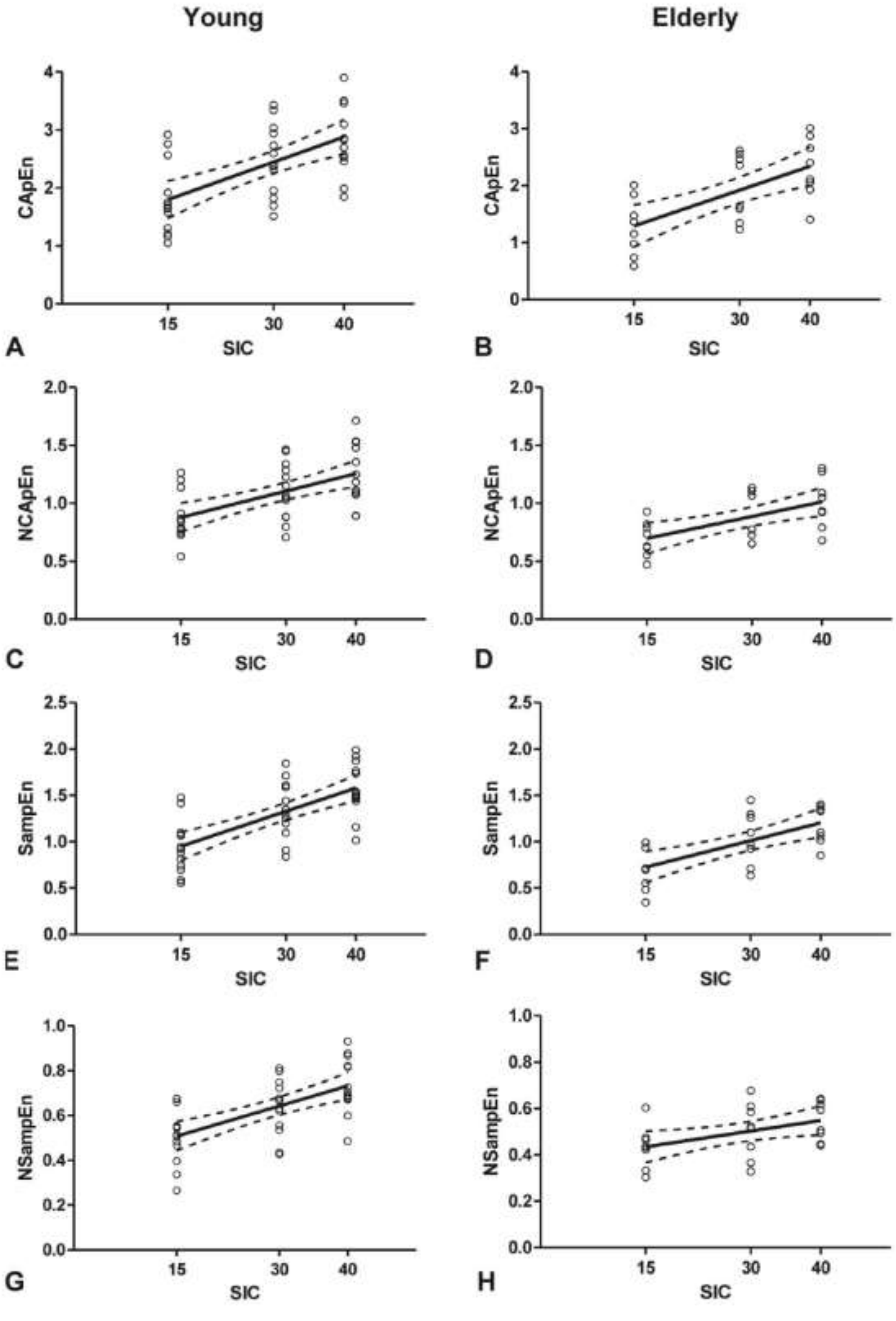

Figure 1. Linear regression of the different % of MVC vs. torque complexity metrics; CApEn in young (A) and old adults (B), NCApEn in young (C) and old adults (D), SampEn in young (E) and old adults (F), and NSampEn in young (G) and old adults (H). MVC = maximum voluntary contraction; SIC = submaximal isometric contraction.

Table 2: Comparison of the linear regression parameters of each variable versus SIC

		YG	OG	p Value
Torque	**Slope**	2.064 ± 0.2856	1.725 ± 0.1781	0.39
	Intercept	2.257 ± 8.607	1.161 ± 5.367	0.009
CApEn	**Slope**	0.043 ± 0.009	0.042 ± 0.01	0.923
	Intercept	1.148 ± 0.284	0.663 ± 0.317	<0.001
NCApEn	**Slope**	0.015 ± 0.004	0.013 ± 0.004	0.648
	Intercept	0.651 ± 0.109	0.508 ± 0.116	<0.001
SampEn	**Slope**	0.025 ± 0.004	0.019 ± 0.005	0.379
	Intercept	0.573 ± 0.134	0.439 ± 0.146	<0.0001
NSampEn	**Slope**	0.009 ± 0.002	0.004 ± 0.002	0.129
	Intercept	0.374 ± 0.057	0.367 ± 0.059	<0.0001

SIC: submaximal isometric contraction; YG: young group; OG: Old group; CApEn: corrected approximate entropy; NCApEn: normalized corrected approximate entropy; SampEn: sample entropy; NSampEn: normalized sample entropy

DISCUSSION

The main findings of this study were that: i) the torque variability was similar between groups, except at the highest force level where the YG exhibited higher values, and ii) the torque complexity increased with the force levels in both groups, and the OG exhibited reduced torque complexity compared to the YG.

As a preliminary observation, the PT of the OG was 26% lower than the YG. This finding is consistent with a previously reported decrease in knee extensor muscle strength in older adults compared with young subjects, although to a lesser extent. For instance, Tracy and Enoka (32) and Christou and Carlton (3) reported that the isometric MVC was 33% and 40% lower, respectively, in older adults compared to young subjects. Therefore, the OG exhibited decreased knee extensor muscle strength, which can be considered as a typical marker of age-related dynapenia in normal aging (12). Both groups exhibited similar torque variability, except at the highest isometric contraction (40% MVC) where the YGs value was higher. Although these findings appear in contrast with those of some studies (15,32), they are consistent with other reports (3). For instance, the findings of Tracy and Enoka (32) supported the hypothesis of the age-related increase in the magnitude of force fluctuations after they compared force fluctuations in young and older adults during submaximal isometric contractions of the knee extensor muscles. Nonetheless, there are some critical methodological differences that prevent direct comparisons with the present study. For example, even though Tracy and Enoka evaluated the same muscle group as the present study, their protocol required subjects to exert low (2, 5 and 10% MVC) and moderate (50% MVC) isometric contractions, which were different from those used in the present study. In addition, the authors concluded that older adults were less steady than young subjects using only the results from the low isometric contractions, as no differences were found in the moderate isometric contractions. In contrast, other studies concluded that force variability was similar between young subjects and older adults during isometric contractions. For instance, Christou and Carlton (3) found no difference in the force variability between young and older adults during isometric contractions performed with the knee extensor muscles across target forces of 5%–90% MVC. These findings are consistent with those of the present study as they identified no differences between the YG and the OG at low isometric contractions (15% and 30% MVC). The torque variability metrics quantify the ability to control muscle force by evaluating the magnitude of fluctuations in torque output. The physiological mechanisms underlying its change with advancing age are not fully understood, however, they are thought to be related to loss of synchronization of motor unit firing, variability in motor unit discharge rate, reduced size of neurons, reduced number of synapses, reduces integrity of gray matter and volume of white matter, and lower neurotransmitter levels (8). Furthermore, evidence suggests that the age-related loss and remodeling of motor units as well as the relative contribution of their recruitment and firing rate vary depending on muscles location and habitual activity (1,6,35). Thus, the known factors underlying the age-related changes in torque variability are likely to vary depending on assessed muscles and physical activity level, for instance. This could explain why previous research has failed to definitively agree on the value of torque variability as a function of age. Briefly, the available findings regarding the force variability changes as a function of age vary between studies, ranging from a significant effect (20) to a nearly significant effect to no difference (3). This emphasizes that the hypothesis of an increased magnitude of torque variability with advancing age is not as straightforward as conventionally thought.

The findings from this study showed that the OG exhibited reduced torque complexity. This is consistent with previous reports and confirms the hypothesis of age-related loss of physiological complexity postulated by Lipsitz and Goldberger (17). However, this study is the first to extend such a hypothesis to the torque of knee extensors. Studies investigating force or torque complexity in aging usually use protocols targeting small muscle groups of the upper limb (33,36). For instance, Vaillancourt and Newell (33) examined the maintenance of force produced during isometric index finger abduction in three groups (young, 20–24 years; old, 60–69 years; and older, 75–90 years) and reported lower force complexity with increasing age. The findings of Vieluf et al. (36) also supported the hypothesis of age-related loss of physiological complexity after comparing the ability of young and older adults to press their right index finger on a force transducer at various target force levels (10, 20, 60, and 80% MVC). The torque complexity metrics provide an insight into the dimensions of feedback control loops governing force output and the underlying state of the neuromotor system (18), which cannot be inferred from torque variability metrics. Evidence suggested that the neuro-physiologically mediated mechanisms underlying age-related loss of force complexity are due to ischemic loss of neuronal tissue, alpha motor neurons and motor units (34), decreased modulation of the descending drive (31) and altered discharge rates and recruitment/de-recruitment potentials of individual and populations of motor units (10). These changes lead to fewer attractors, reduced number of control processes, with or without decoupling of control processes (23,27,29). Thus, with advancing age, there is a shift from multiple and equally-operating neural oscillators operating across multiple time scales to fewer, stronger, and more dominating neural oscillators operating across fewer time scales (30). In other words, the aging process triggers a reduction of the adaptive flexibility to coordinate the excitatory and inhibitory properties of the neural oscillators that input to the motor neuron pool. Thus, older adults are less able to regulate each of these neural oscillators in a coordinative output to match the required task demand (13).

This results in more structured force output, relatively fixed or stereotypic patterns in motor coordination associated with impaired functional components.

In young subjects, at low levels of intrinsic hand muscles contraction, force is increased mainly by increasing the number of active motor units; however, once all motor units are recruited, further increases in force are achieved through increases in the firing rate of the recruited motor units (11). Therefore, both neural mechanisms are available at around 30–40% MVC, which gives the neuromuscular system the broadest possibility of adapting the force output to the force target. Hence, when older adults perform muscle contractions, it could be expected that, as consequence of the age-related decreased number of motor units (19), the most of the remaining motor units are recruited at lower force levels than in young subjects. Then, it is necessary to increase the firing rate of these recruited motor units at lesser force levels than in young subjects. Thus, both neural control strategies would be available at a force region lower than in young subjects. Accordingly, it was initially hypothesized that, in older adults, as a function of force level, knee extensors torque complexity would follow a steeper slop with maximum value observed at lesser force levels than in young subjects (i.e. below 30-40% MVC). However, the major novel finding of this investigation was that, although the torque complexity of the knee extensor was reduced in older adults, its relationship with the contraction intensity was similar in both groups, with maximum values of complexity observed at 40% MVC. This suggests that the organization of the knee extensors' force control is preserved in older adults. The specific mechanisms underlying the relationship between torque complexity and contraction intensity in larger postural muscles of healthy older adults are unknown since this is the first study extending such relationship to knee extensors in this population. Studies suggested that with advancing age, loss and remodeling of motor units are delayed and mitigated in habitually active postural muscles, up to a critical age-related threshold (6,35). Thus, the findings from this investigation could be attributed to an attenuated loss of motor units within the knee extensors muscles of the OG, such that, the remaining motor units are beyond the critical threshold required to increase muscular force only through motor unit recruitment up to force levels similar in young subjects (i.e. just below 40% MVC). Once all motor units are recruited, further increases in force are achieved through increases in the firing rate of the recruited motor units such that both neural control strategies are available at 40% MVC (as in young subjects). Slifkin and Newell (28) proposed that the higher values of force complexity as function of force levels coincide with the range of force where the motor performance is optimized. Therefore, in the current study, it appears that the motor performance of the knee extensors is optimized at similar range of force in young subjects and healthy older adults.

Some limitations of this study should be emphasized. First, the current study assessed the relationship between the knee extensor torque complexity and the contraction intensity across target forces up to just below the force midrange. However, studying a greater range of force (e.g., 5%–90% MVC) would provide more information about the characteristics of the neural mechanisms involved in the organization of the force control system. Afterward, instead of consecutive fixed order, performing the contractions in random order would be a better approach to minimize eventual bias. In addition to knee extensor torque output assessment, records and analyses of the electromyographic activities of knee extensor muscles would provide a better understanding of the behavior of neural properties (e.g., motor unit recruitment, firing rate, etc.) during the studied task.

PRACTICAL APPLICATIONS

This investigation examined the force complexity of large postural muscles (i.e., knee extensors) in older adults by assessing its relationship with force levels. It appears that aging is accompanied by reduced torque complexity although the pattern of the relationship between knee extensor torque complexity and force levels are similar. Besides providing further evidence about the characteristic loss of muscle strength and impaired motor control repeatedly observed in larger postural muscles of older adults, these findings mainly suggest that the motor performance of the knee extensors muscles is optimized at the same force levels (40% MVC) in healthy older adults and young subjects. This means that, when performed at such intensities, knee extensors contraction is supported by more neural control strategies than in lower intensities. Accordingly, it may be suggested that repeated contractions performed at such intensities (for instance as part of an exercise training program) would repeatedly activate these neural control strategies with a consequent force control improvement. However, further investigations examining greater range of force (e.g., 5%–90% MVC) would be particularly relevant to determinate the intensity as well as other intervention parameters such as training modality, frequency and duration.

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ESTUDO II

(Versão em inglês apresentada nas normas da revista)

EXERCISE TRAINING IN OLDER ADULTS, WHAT EFFECTS ON MUSCLE FORCE CONTROL? A SYSTEMATIC REVIEW OF RANDOMIZED CLINICAL TRIALS

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ABSTRACT

Aim: To determine the magnitude of the effects of different exercise training (ET) modalities on variables of muscle force control in older adults. **Methods:** Relevant articles were searched in PubMed, Web of Science, Science Direct and Scopus, using the keywords: Aged AND (“Exercise Movement Techniques” OR Hydrotherapy) AND ("Complexity of torque" OR "Complexity of force" OR "Variability of torque" OR "Variability of force" OR "Force Steadiness" OR "Force fluctuations"). To be included in the full analysis, the studies had to be randomized controlled trials in which older adults were submitted to ET programs and muscle force control assessment. **Results:** The searches resulted in 731 articles from which 6 met all the inclusion criteria. The trials involved 171 healthy and functionally limited older adults (71.64±1.53 years). Studies included resistance, steadiness and functional training programs. Training sessions were 2–3 time per week, lasted 6-16 months with intensities determined as percentage of the one repetition maximum loads. There is a heterogeneity regarding experimental set-up and data analysis parameters between studies. The findings suggested an improved muscle force control in older adults after ET. However, the quality of evidence of the published clinical trials showed that the confidence about such an improvement is limited for the knee extensor muscle force and very limited for dorsal interosseus muscles force. **Conclusions:** The findings from this review suggest that ET programs are effective to improve muscle force control in older adults. However, future studies are likely to impact the confidence in such effects.

Key-words: aged; exercise movements technique; muscle force control.

1. INTRODUCTION

The process of aging is accompanied by structural changes in the neuromuscular system including reduced number of motor units (Dalton, McNeil, Doherty, & Rice, 2008), altered fiber type distribution (Lexell, 1995) and reduced muscle cross-sectional area (Kent-Braun & Ng, 1999). Often, such changes are investigated through parameters of maximal performance such as the maximal force (Caserotti, Aagaard, Buttrup Larsen, & Puggaard, 2008; Thompson et al., 2014). However, muscle maximal force measurement yields a narrow comprehension of the age-related changes within the neuromuscular system. For instance, it fails to provide information about the neurophysiologically mediated mechanisms underlying the decline in motor task accuracy and functional capacities with advancing age. Indeed, although increasing maximal force is an important issue in older adults, the literature shows that the gains of maximal force in response to exercise training (ET) programs are often not related to improvement in functional capacities (Chandler, Duncan, Kochersberger, & Studenski, 1998; Izquierdo, Aguado, Gonzalez, López, & Häkkinen, 1999; Ringsberg, Gerdhem, Johansson, & Obrant, 1999). Rather, it has been demonstrated that the age-related declines in functional capacities are more closely a matter of an impaired ability to control muscle force than a reduced capacity to generate maximal force (Shepard, Schultz, Alexander, Gu, & Boismier, 1993).

The force exerted by a muscle during a voluntary contraction is regulated by several neuromuscular mechanisms (e.g. mechanical summation of motor unit forces, pattern of output from the motoneuron pool) (Roger M. Enoka et al., 2003). Consequently, the muscle force is not constant, but rather it fluctuates about an average value (Dietz, Bischofberger, Wita, & Freund, 1976; Galganski, Fuglevand, & Enoka, 1993; Löscher & Gallasch, 1993; Slifkin & Newell, 1999). The analysis of such fluctuations during standardized tasks (i.e. submaximal isometric, shortening and lengthening contractions) become a widely used method to assess the ability to control muscle force (Laidlaw, Bilodeau, & Enoka, 2000; Lodha, Naik, Coombes, & Cauraugh, 2010; D E Vaillancourt, Slifkin, & Newell, 2002). Routinely, studies investigate the muscle force control by assessing the variability of the force output through statistical metrics in absolute (within-subject standard deviation; SD) and relative (coefficient of variation; CV) terms (Contessa, Adam, & De Luca, 2009). Higher values mean higher variability of force that is a poor muscle force control. However, because of the interactions between the components of the neuromuscular system, the force output fluctuates according to an irregular, non-linear and chaotic (complex) behavior (David E. Vaillancourt & Newell, 2003) whose temporal structure can't be analyzed through classic statistical metrics. Thereby, besides simple measures of the variability of force, it has been proposed to analyze the series of force output using methods derived from non-linear dynamics, based on chaos theory such as approximate entropy (ApEn) (Pincus, 1991) and sample entropy (SampEn) (Richman & Moorman, 2000). Higher values mean greater complexity that is a better muscle force control. While the measures of the variability of force only quantify the ability to control muscle force through the magnitude of fluctuations in force output, the measures of the complexity of force provide an insight into the dimensions of feedback control loops governing force output and the underlying state of the neuromotor system (Mayer-Kress, Deutsch, & Newell, 2003), which cannot be inferred from statistical metrics.

It is established that aging is characterized by a declined muscle force control evidenced by a heightened variability and decreased complexity of force (S. P. Arjunan, Kumar, & Bastos, 2012; Sridhar P. Arjunan & Kumar, 2013). Such age-related loss of muscle force control has been shown to contribute to the wide related reduced ability of the older adults to execute precise motor tasks common to daily living, including handwriting, object manipulation and cooking (Flanagan & Wing, 1993; Johansson, 2002) as well as self-lifting and postural balance. Exercise programs have been investigated in order to be used as therapeutic strategy in the management of age-related decline of motor task accuracy and muscle force control (B K Barry & Carson, 2004). However, the effectiveness of ET programs on muscle force control remains uncertain since the available evidence relate contrasting findings depending on studies characteristics (i.e. subjects clinical status, assessed muscles, experimental set-up, data analysis parameters and ET modalities). This seems to be an important issue since providing evidence about the effectiveness of ET programs to improve muscle force control could be helpfull for prescribing the most suitable exercise modality in the management of age-related declines of motor task accuracy and muscle force control.

This study aimed to determine the magnitude of the effects of different ET modalities on variables of muscle force control in older adults, through a systematic review of literature. In addition, this study aimed to evaluate, through the GRADE approach, the quality of the evidence of the published clinical trials investigating the effectiveness of ET programs on the muscle force control of older adults.

2. METHODS

This systematic review is registered in PROSPERO, an international database of prospectively registered systematic reviews in health and social care.

2.1. Search strategy and identification of trials

Searches were conducted in 4 electronic databases; PubMed, Web of Science, Science Direct and Scopus, the following keywords and Medical Subject Headings were used in the search: *Aged AND ("Exercise Movement Techniques" OR Hydrotherapy)*

AND ("Complexity of torque" OR "Complexity of force" OR "Variability of torque" OR "Variability of force" OR "Force Steadiness" OR "Force fluctuations"). There were no restrictions concerning the publication date but the results were limited to English and Portuguese language.

One author performed the searches and the results were forwarded from each electronic database to the StArt tool (version 2.3.4.2), a Systematic Review tool support that allows the centralization of the databank results, automatic identification of redundant trials and easiest management of trials selection and extraction process (Hernandes, Zamboni, Fabbri, & Thommazo, 2012). Then, two authors independently assessed the title and the abstract of each article through the StArt tool, excluding irrelevant trials in accordance with the inclusion criteria. Afterwards, a full-text review and a methodologic appraisal were performed. After each selection step; title, abstract and full-text evaluation successively, both authors checked the agreement of their databank of accepted trials. A discussion involving the third reviewer was conducted in the event of disagreement.

Further, after the selection process, reference lists from the selected articles were checked to retrieve articles that met the inclusion criteria but were not found during the inicial searches in the electronic databases (Fabbri et al., 2016). This latter process was repeated until no article fulfilling the inclusion criteria was found. In order to find relevant recent studies, additional searches on the 4 initial electronic databases were repeated with the same keywords and Medical Subject Headings. This process was done until the end of the preparation of the manuscript.

2.2. Eligibility criteria for study selection

The studies included in this systematic review met the following criteria.

Study design. Only randomized clinical trials were included.

Participants. It has been adopted the definition of older adults as person over 65 years old (Quadagno, 2002). Then, only samples with a mean age of at least 65 years were included. The mean age, sample size and clinical status were recorded.

Type of intervention. Subjects participated in a ET program with single or multiple components. The intensity, duration, frequency, type and length of exercise in each article were recorded.

Outcome measures. Studies reporting outcomes related to muscle force control (i.e. force variability and/or complexity) assessed by analyzing force signals recorded during submaximal isometric contractions. The experimental set-up and parameters of the investigated variables were recorded.

2.3. Methodologic quality assessment

Each paper was critically appraised by 2 reviewers for methodologic quality by using the Physiotherapy Evidence Database (PEDro) scale (0–10) (de Morton, 2009; Maher, Sherrington, Herbert, Moseley, & Elkins, 2003). Higher PEDro scores indicated better quality. The literature suggests that high-quality studies should achieve a total score higher than 50% of the possible maximum (Coury, Moreira, & Dias, n.d.; Verhagen et al., 1998). Thus, for this review, trials with a PEDro score higher than or equal to 5.0 were classified as high methodological quality studies.

2.4. Data extraction

Two authors independently extracted following relevant data from included studies: participants’ data (sample size, mean age, studied groups and clinical status), ET program parameters (intensity, duration, frequency, type and length of exercise), experimental set-up and parameters of the investigated variables. The differences were discussed with the third author. The result sections of each article were studied and all relevant results related to the training intervention effects on the main outcomes were extracted and interpreted.

2.5. Data synthesis and analysis

The heterogeneity of the included clinical trials (regarding the parameters of ET programs, experimental setup and data analysis) hindered to perform a meta-analysis. The magnitude of the effect of each ET program on the investigated variables was assessed throught the effect size (ES). Standardised mean difference (Larry Hedges & Ingram Olkin, 2014) was calculated for each comparison group separately, considering the values before and after intervention. These were further classified as small (<0.20), moderate (around 0.50) or large (>0.80), according to Cohen's criteria (Cohen, 1988).

The quality of evidence for the outcomes standard deviation (SD) and coefficient of variation (CV) was determined through the GRADE approach. The GRADE approach classifies the level of evidence as high, moderate, low, or very low analysing the following domains that can affect the quality of the evidence of the outcomes of a clinical trial: trial design limitations due to risk of bias, inconsistency of results, indirectness, imprecision of results and publication bias. A review of each factor followed the subsequent classification: not serious (score is not rated down), serious (score is rated down by one level) and very serious (score is rated down by two levels), according to the interference biases detected in these items. The details of this method have been reported previously (Atkins et al., 2004; Furlan, Pennick, Bombardier, van Tulder, & Editorial Board, 2009; Richards et al., 2013).

3. RESULTS

3.1. Trial selection

The searches in electronic databases resulted in 731 clinical trials, of which 70 were duplicated and 232 excluded by title checking, remaining 429 articles. From these, 424 were rejected after the abstract evaluation, remaining 5 selected articles. After checking the references of these, 201 articles were found. 200 of these latter were excluded after evaluation, resulting in 1 new selected article. After checking the references of this article, 25 articles were found. From these, 22 were rejected and 3 duplicated, remaining no article. Summarily, the initial searches and the references checking resulted in 6 articles. Details of the selection process are presented in Fig. 1.

3.2. Characteristics of included studies (Table 1)

3.2.1. Participants

The studies involved 171 older adults with mean age of 71.64 ±1.53 years old. Most of the subjects were female (62.38%), and two studies did not report participants gender (Hortobágyi, Tunnel, Moody, Beam, & DeVita, 2001; Tracy & Enoka, 2006). One study involved functionally limited older adults (Manini, Clark, Tracy, Burke, & Ploutz-Snyder, 2005) while in others studies, participants were healthy older adults. In all trials, participants were divided in training and control groups. The findings of Hortobágyi et al. included older adults and young subjects (Hortobágyi et al., 2001), although, only older adults' results have been analyzed in this review.

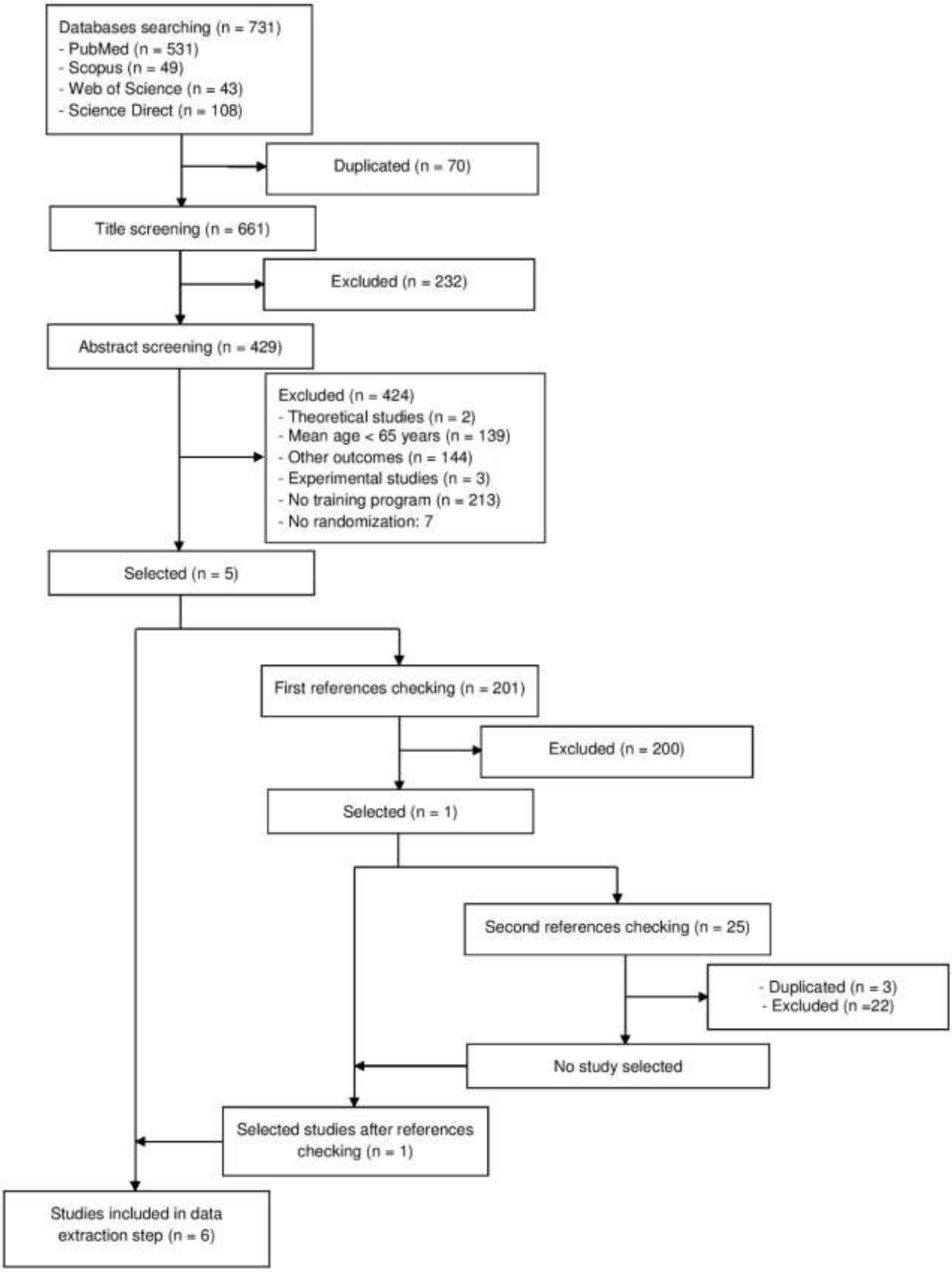

Figure 1. Flowchart for the search strategy and reasons for exclusion

Table 1. Characteristics of the included studies

Studies	Participants (clinical status, group, Sample size, gender, age)	Intervention (training modality, intensity, frequency and duration)	Assessed muscles	Experimental set-up
Hortobágyi *et al.* (2001)	Healthy old adults (n = 30; M&F*; 72±4.7 years) and young (n = 10; M&F*; 21.1±1.2).	30 sessions of strength training using bilateral supine leg press as the exercise. HI Group: 5 bouts of 4-6 repetitions with 80% of the 1-RM. LI Group: 5 bouts of 8 to 12 repetitions at 40% of their maximal weight.	Knee extensor muscles	Subjects were instructed to sustain contractions at 25 N during 5 seconds.
Kobayashi et al. (2012)	Healthy older adults; Training group (n = 17; M:7; F:10; 67.5±5.2 years) and Control group (n = 7; M:3; F:4; 67.5±5.8 years)	8 weeks of BML training performed on BML training machines; 3 d/week; at 30% of the 1-RM in 5-7 sets of 15 repetitions.	Knee extensor muscles and elbow flexors muscle	Steady contractions at three target forces: 10%, 30%, and 65% MVCs performed in random order and sustained for 10-12 seconds with at least 60s of rest between trials.
Manini et al. (2005)	Functionally limited older adults; RT (n = 9; M:1; F:8; 72±10 years); FT (n = 8 F; 79.2±7.5 years) and FRT (n = 7; M:1; F:6; 73±5.5 years)	10 weeks of RT (three lower body exercises: leg press, leg extension and leg curl), FT (rising from a chair, rising from a kneeling position and stair ascending/descending) or FRT; performed 2 days/week; each session lasted 30–45 min. RT: 2 training sets of 10RM. Once a subject was able to lift more than 10 repetitions the load was increased. If the subject was unable to lift the weight for 8 repetitions, the load was decreased. FT: 2 work sets with 10 repetitions. FRT: 1day of resistance and 1day of functional training per week.	Knee extensor muscles	Subjects were asked to exert a knee extension force to a target level during 15 seconds, with their dominant limb at three different intensities (10, 25 and 50% MVC) in a random order.

Table 1: (Continued)

Studies	Participants (clinical status, group, Sample size, gender, age)	Intervention (training modality, intensity, frequency and duration)	Assessed muscles	Torque variability/complexity assessment methods
Tracy & Enoka (2005)	Healthy old adults, Training group (n = 21) and Control group (n = 9); 72±4.6 years	16 weeks of knee-extension exercise training using weight-stack machine (Icarian, Sun Valley, CA), 3 d/week at 30% of 1-RM (adjusted weekly) 3 sets of 10 repetitions of the knee-extension exercise.	Knee extensor muscles	The participants performed a knee extension as steady as possible for 10-12 seconds, at target forces of 2, 5, 10, and 50% of MVC force with the left leg.
Tracy et al. (2003)	Healthy old adults; Heavy-load strength training (n=11; M:5; F:6; 73.1±4.9 years), Heavy-load steadiness training (n=6; M:4; F:2; 69.7±3.7 years) and Control Group (n=9; M:4; F:5; 74.2±4.9 years).	16 weeks of heavy-load strength training or heavy-load steadiness training, performed 3 d/week at 3 sets of 10 repetitions of a knee-extension task. Heavy-Load and Heavy-Load Steady training: 80% of 1-RM load. Updated weekly.	Knee extensor muscles	After the MVC assessment, isometric knee extension contractions were performed with the left leg at target forces of 2, 5, 10, and 50% MVC. Subjects were instructed to match the target as steadily as possible for 10–12 s.
Laidlaw et al. (1999)	Old adults with no known neuromuscular disorders heavy-load training group (n = 8; M:4; F:4; 68.3±2.2 years); light-load training group (n = 8; M:4; F:4; 70.4±2.0 years) and control group (n = 11; M:5; F:11; 72.4±1.7 years)	4 weeks of strength training program with the first dorsal interosseus muscle, 3 d/week. 6 sets of 10 repetitions. The heavy-load group: 80% of the 1-RM load, and the light-load group: 10% of the 1-RM load. The 1-RM load was measured weekly, and the training loads were set accordingly.	The first dorsal interosseus	After the MVC in the abduction direction. Target forces were set at 2.5, 5, 10, and 20% of MVC force. The subjects gradually increased the abduction force during an isometric contraction to the target force displayed on the oscilloscope and held the force steady at the target force for 30 s. The order of the trials was varied.

M: Male; F: Female; LI: Low Intensity; HI: High Intensity; BML: Beginning Movement Load; MVC: Maximum Voluntary Contraction; RM: Repetition-Maximum; RT: Resistance Training; FT: Functional Training; FRT: Functional + Resistance Training.

3.2.2. Interventions

The most of the trials included resistance training (Hortobágyi et al., 2001; Kobayashi, Koyama, Enoka, & Suzuki, 2014; Laidlaw, Kornatz, Keen, Suzuki, & Enoka, 1999; Manini et al., 2005; Tracy, Byrnes, & Enoka, 2004; Tracy & Enoka, 2006). The other ET programs were steadiness (Tracy et al., 2004) and functional (Manini et al., 2005) training programs. Resistance training programs targeted on the knee extensor, elbow, wrist and hand muscles. Depending on the trials, training sessions were 2 to 3 time per week, for 6 to 16 weeks with training intensities determined as percentage of the one repetition maximum (1-RM) loads. Across studies, participants performed 2 to 7 sets of 8 to 12 repetitions through direct loads or specifics training devices: beginning movement load machine (Kobayashi et al., 2014) and weight-stack machine (Tracy & Enoka, 2006).

3.2.3. Experimental set-up

The force control was assessed for the knee extensor muscle (Hortobágyi et al., 2001; Kobayashi et al., 2014; Manini et al., 2005; Tracy et al., 2004; Tracy & Enoka, 2006), elbow flexors muscle (Kobayashi et al., 2014) and dorsal interosseus (Laidlaw et al., 1999). After determining the individual isometric MVC, participants were required to sustain contractions at different target forces calculated as percentage of the MVC, except Hortobagyi et al, who defined a fixed target force (25N) for all subjects (Hortobágyi et al., 2001). In the trials which investigated the force control of the knee extensor muscle, participants were positioned on an isokinetic dynamometer with the knee angle varying between 65° and 95° of knee flexion (full extension = 180°) depending on studies. Participants were required to sustain submaximal contractions at target forces between 2% and 65% of their MVC during 5 to 15 seconds. The contractions were performed in random order and each contraction was followed by a 60-second rest period. In the trial which investigated the force control of hand muscles, the target forces were between 2.5%, 5%, 10% and 20% of MVC and participants were required to exert isometric contractions during 30 seconds on load cells connected to strain-gauge amplifiers. Participants rested for 60–90 s between consecutive contractions (Laidlaw et al., 1999). Only one study investigated the force control of elbow flexors muscle (Kobayashi et al., 2014). In this study, the elbow joint of the right arm was flexed to 90° (full extension angle: 180°). The participants were required to sustain submaximal contractions at 10%, 30% and 65% of their MVC during 10-12 seconds in random order with at least 60 s of rest between trials (Kobayashi et al., 2014).

3.2.4. Data analysis

The force control of the knee extensor muscle was assessed by analyzing the steadiest 1 to 8 seconds windows from the central region of the force signals. The sampling frequency varied between 200 to 1000 Hz depending of studies. Therefore, the total data points assessed were 1600 (Kobayashi et al., 2014; Tracy et al., 2004; Tracy & Enoka, 2006) and 8000 (Manini et al., 2005). Hortobagyi et al, assessed separately 1000 and 5000 data points (Hortobágyi et al., 2001). The studies investigated the knee extensor variability through both SD and CV of the force signals, except Hortobagyi et al who preferred only the latter variable (Hortobágyi et al., 2001). Besides the CV of the force signals, Kobayashi et al also assessed the knee extensor variability by analyzing in the frequency domain of the force signals with fast Fourier transform (FFT) analysis (Kobayashi et al., 2014). The force control of the dorsal interosseus muscles was investigated by analyzing the 20 seconds steadiest windows from the central region of the force signals, however, the sampling frequency has not been reported, therefore, the total data points analyzed was unknown (Laidlaw et al., 1999). Authors investigated the force variability through both SD and CV of the force signals. Kobayashi et al. assessed the force variability of elbow flexors muscle by computing the CV and analyzing the frequency domain of the force signals with FFT analysis. The authors analyzed the steadiest 8 seconds windows from the central region of the force signals. The sampling frequency was 200 Hz, thus, the total data points assessed were 1600 (Kobayashi et al., 2014).

3.3. Quality assessment

PEDro average score was 6.5, ranged from 6 to 7. The most critical criteria to be satisfied were secret allocation and participants, therapist and assessor blinding (Table 2).

Table 2. PEDro Scale of the Included Studies

Study	Specified Eligibility Criteria	Random Allocation	Secret Allocation	Similar groups at baseline	Participants Blinding	Therapist Blinding	Assessor Blinding	< 15% Dropouts	Intention-to-Treat Analysis	Between-Group Difference Reported	Point Estimate and Variability Reported	PEDro Score (0–10)
Hortobagyi *et al.*(2001)	1	1	0	1	0	0	0	1	1	1	1	7
Kobayashi *et al.*(2012)	1	1	0	1	0	0	0	0	1	1	1	6
Manini *et al.*(2005)	1	1	0	1	0	0	0	0	1	1	1	6
Tracy & Enoka (2005)	1	1	0	1	0	0	0	1	1	1	1	7
Tracy *et al.*(2003)	1	1	0	1	0	0	0	1	1	1	1	7
Laidlaw *et al.*(1999)	0	1	0	1	0	0	0	1	1	1	1	6
Studies which satisfied the criteria (%)	83.33	100	0	100	0	0	0	66.67	100	100	100	

3.4. Effects of exercise

The magnitude of the effect of each ET program on the muscle MVC and force control is presented on the Table 3. Briefly, although some trials failed to show a significant increase of the MVC after training, the findings showed that the ET programs have large effects on the MVC of older adults regardless the participants clinical status, assessed muscles, experimental set-up and the exercise modalities. Across studies, depending on the force targets and ET programs, the SD of the force signals increased (Tracy et al., 2004) or decreased (Laidlaw et al., 1999; Tracy et al., 2004) significantly. Mostly, the studies reported that the exercise-related changes in the SD were non-significant (Hortobágyi et al., 2001; Laidlaw et al., 1999; Manini et al., 2005; Tracy & Enoka, 2006). The calculated effect sizes depended on the force targets and exercise modalities. Resistance training programs showed both negatively (Laidlaw et al., 1999; Manini et al., 2005) and positively (Hortobágyi et al., 2001; Tracy et al., 2004) small to large effects on the changes of the SD of the force signals. Functional (Manini et al., 2005) and steadiness (Tracy et al., 2004) training mainly showed positively small to large effects on the changes of the SD of the force signals. Studies reported significant decreases of the CV of the force signals after training (Kobayashi et al., 2014; Laidlaw et al., 1999; Tracy et al., 2004), although in one trial such exercise-related changes of CV were non-significant (Manini et al., 2005). Nevertheless, the calculated effect sizes showed that regardless participants clinical status, assessed muscles, experimental set-up and the exercise modalities, ET programs have mainly negatively small to large effects in the decreases of the CV of the force signals.

Previously to assess the quality of evidence for the outcomes, the trials included in the systematic review were divided according to the assessed muscles (knee extensor and dorsal interosseus muscles). Subsequently, since the outcomes (SD and CV) are related to force targets, the GRADE approach don’t included one study in which a fixed force target (25 N) was established for all participants instead of being determinated by calculating a percentage of the individual MVC (Hortobágyi et al., 2001). Furthermore, one study without untrained control group was not included in the GRADE approach (Manini et al., 2005). Therefore, the 4 remaining trials were included in the assessment of the quality of evidence for the outcomes (Kobayashi et al., 2014; Laidlaw et al., 1999; Tracy et al., 2004; Tracy & Enoka, 2006). In the remaining studies, distinctions were made according to the force targets and comparison groups.

The quality of evidence for each outcome according to the GRADE approach is presented in Table 4a, Table 4b, Table 5a and Table 5b. Reasons for downgrading the quality of the body of evidence are cited in the notes below each table. Briefly, the quality of the body of evidence of resistance training contribution programs on the decrease of SD and CV of force signals was low and very low respectively for knee extensor muscle and dorsal interosseus muscles in older adults.

Table 3. Magnitude of the effect of training programs on mucle force control

Studies	Groups	MVC (Cohen's d)	Force targets (%)	SD (Cohen's d)	CV (Cohen's d)
Hortobagyi *et al.* (2001) ‡	Low Intensity Training Group	↑ 1.74	25 N (1s)	↑ 1.63	NA
			25 N (5s)	↑ 0.82	NA
	High intensity Training Group	↑ 2.78	25 N (1s)	0	NA
			25 N (5s)	0	NA
	Combined Training Group	↑ 2.26*	25 N(1s)	0	NA
			25 N (5s)	0	NA
	Control Group	↑ 0.34	25N(1s)	0	NA
			25N (5s)	0	NA
Kobayashi *et al.* (2012)	BML Training Group (Knee Results)	↑*	10	NA	↓* 2.2
			30	NA	↓* 2.16
			65	NA	↓* 2.97
	Control Group (Knee Results)	↑	10	NA	↑ 0.06
			30	NA	↓ 1.23
			65	NA	↑ 0.09
	BML Training Group (Elbow Results)	↑	10	NA	↓* 1.99
			30	NA	↓* 1.72
			65	NA	↓* 1.95
	Control Group (Elbow Results)	↑	10	NA	↑ 1.22
			30	NA	↑ 0.03
			65	NA	↑ 0.1

Table 3. (Continued)

Studies	Groups	MVC (Cohen's d)	Force targets (%)	SD (Cohen's d)	CV (Cohen's d)
Manini *et al.* (2005)	Resistance Training Group	↑* 0.56	10	↓ 0.25	↓ 0.20
			25	↓ 0.00	↓ 0.57
			50	↓ 0.11	↓ 0.50
	Functional Training Group	↑* 0.83	10	↑ 0.47	↑ 0.28
			25	↓ 0.17	↓ 0.44
			50	↑ 0.21	↓ 0.48
	Functional + Resistance Training Group	↑* 0.46	10	↓ 0.33	↓ 0.30
			25	↓ 0.59	↓ 0.46
			50	↓ 0.22	↓ 0.36
Tracy & Enoka (2005)	Training Group	↑* 0.71	2	=	=
			5	=	=
			10	=	=
			50	=	=
	Control Group	↑ 0.17	2	=	=
			5	=	=

Table 3. (Continued)

Studies	Groups	MVC (Cohen's d)	Force targets (%)	SD (Cohen's d)	CV (Cohen's d)
Tracy *et al.* (2003)	Steadiness Training Group	↑* 1.25	2	↑ 1.1	↑ 0.18
			5	↓* 12.88	↓ 1.49
			10	↑* 0.92	↓ 0.37
			50	↑ 0.22	↓* 1.16
	Strength Training Group	↑* 1.25	2	↓ 0.30	↓ 0.73
			5	↑* 0.82	↓ 0.38
			10	↑ 0.66	↓0.24
			50	↑ 1.17	↓ 0.26
	Control Group	↑ 0.17	2	↓ 0.48	↓ 0.37
			5	↓ 0.32	↓ 1.11
			10	↑ 0.86	↑ 0.21
			50	↓ 1.07	↓ 0.83
Laidlaw *et al.* (1999)	Light Load Training Group	↑* 2.5	2.5	↓ 1.64	↓* 2.5
			5	↓ 1.41	↓* 2.3
			10	↓ 8.59	↓* 5.61
			20	↓* 12.19	↓* 7.99
	Heavy Load Training Group	↑* 4.44	2.5	↓ 3.91	↓* 17.14
			5	↓ 3.1	↓* 5.17
			10	↓ 3.74	↓* 9.28
			20	↓* 8.3	↓* 35.07
	Control Group	↑ 1.31	2.5	↓ 0.94	↓ 0.88
			5	↓ 0.68	↓ 1.87
			10	↓ 1.49	↓ 6.69
			20	↓ 0.83	↓ 2.05

MVC: Maximum Voluntary Contraction, SD: Standard Deviation, CV: Coefficient of Variation ↑: Positive effect size; ↓: Negative effect size; *: Significant Difference, =: Available data did not allow the effect size calculation, although, authors related that variables remained unchanged, NA: (Not Available) variable not investigated by the study, ‡: fixed force target.

Table 4a. Assessment of quality of evidence based on GRADE approach for studies investigating the standard deviation of the force signal of knee extensor muscle

Certainty assessment							Summary of findings		
Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	Comparator	Quality of evidence
SD of force signal at 2% MVC	2 RCT (Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Not serious	Not serious	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	LOW [d] ⊕⊕◯◯
SD of force signal at 5% MVC	2 RCT (Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Serious (-1) [a]	Not serious	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	LOW [d] ⊕⊕◯◯
SD of force signal at 10% MVC	2 RCT (Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Not serious	Not serious	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	LOW [d] ⊕⊕◯◯
SD of force signal at 50% MVC	2 RCT (Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Not serious	Not serious	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	LOW [d] ⊕⊕◯◯

NOTES: [a]: There was heterogeneity in the results between trials, score was rated down by one level (-1); [b]: The sample sizes were not justified by sample sized calculation, score was rated down by one level (-1); [c]: studies achieved by the same research group and likely based on the same participants, score was rated down by one level (-1); [d]: GRADE working Group grades of evidence: low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ABBREVIATIONS: SD: Standard Deviation of force signal; MVC: Maximum Voluntary Contraction; RCT: Randomized Controlled Trial.

Table 4b. Assessment of quality of evidence based on GRADE approach for studies investigating the coefficient of variation of the force signal of knee extensor muscle

Certainty assessment							Summary of findings		
Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	Comparator	Quality of evidence
CV of force signal at 2% MVC	2 RCT (Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Not serious	Not serious	Serious (-1) [c]	Strongly suspected (-1) [d]	Resistance Training	Untrained	LOW [f] ⊕⊕◯◯
CV of force signal at 5% MVC	2 RCT (Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Not serious	Not serious	Serious (-1) [c]	Strongly suspected (-1) [d]	Resistance Training	Untrained	LOW [f] ⊕⊕◯◯
CV of force signal at 10% MVC	3 RCT (Kobayashi et al., 2012; Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Not serious	Serious (-1) [b]	Serious (-1) [c]	Undetected	Resistance Training	Untrained	LOW [f] ⊕⊕◯◯
CV of force signal at 30% MVC	1 RCT (Kobayashi et al., 2012)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [c]	Strongly suspected (-1) [a]	Resistance Training	Untrained	LOW [f] ⊕⊕◯◯
CV of force signal at 50% MVC	2 RCT (Tracy & Enoka, 2005; Tracy et al., 2003)	Not serious	Not serious	Not serious	Serious (-1) [c]	Strongly suspected (-1) [d]	Resistance Training	Untrained	LOW [f] ⊕⊕◯◯
CV of force signal at 65% MVC	1 RCT (Kobayashi et al., 2012)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [c]	Strongly suspected (-1) [a]	Resistance Training	Untrained	LOW [f] ⊕⊕◯◯

NOTES: [a]: Only one study for this outcome, a one-level rated down score ws assumed for this criteria (-1); [b]: There was heterogeneity in interventions between trials, score was rated down by one level (-1); [c]: The sample sizes were not justified by sample sized calculation, score was rated down by one level (-1); [d]: studies achieved by the same research group and likely based on the same participants, score was rated down by one level (-1); [e]: GRADE working Group grades of evidence: moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; [f]: GRADE working Group grades of evidence: low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

ABBREVIATIONS: CV: Coefficient of Variation of force signal; MVC: Maximum Voluntary Contraction; RCT: Randomized Controlled Trial.

Table 5a. Assessment of quality of evidence based on GRADE approach for studies investigating the standard deviation of the force signal of dorsal interosseus muscles

Certainty assessment							Summary of findings		
Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	Comparator	Quality of evidence
SD of force signal at 2.5% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯
SD of force signal at 5% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯
SD of force signal at 10% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯
SD of force signal at 20% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯

NOTES: [a]: Only one study for this outcome, a one-level rated down score ws assumed for this criteria (-1); [b]: The sample sizes were not justified by sample sized calculation, score was rated down by one level (-1); [c]: studies achieved by the same research group and likely based on the same participants, score was rated down by one level (-1); [d]: GRADE working Group grades of evidence: very low quality: we are very uncertain about the estimate.

ABBREVIATIONS: SD: Standard Deviation of force signal; MVC: Maximum Voluntary Contraction; RCT: Randomized Controlled Trial.

Table 5b. Assessment of quality of evidence based on GRADE approach for studies investigating the coefficient of variation of the force signal of dorsal interosseus muscles

Certainty assessment							Summary of findings		
Outcome	Number of studies	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Intervention	Comparator	Quality of evidence
CV of force signal at 2.5% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯
CV of force signal at 5% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯
CV of force signal at 10% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯
CV of force signal at 20% MVC	1 RCT (Laidlaw et al., 1999)	Not serious	Serious (-1) [a]	Serious (-1) [a]	Serious (-1) [b]	Strongly suspected (-1) [c]	Resistance Training	Untrained	VERY LOW [d] ⊕◯◯◯

NOTES: [a]: Only one study for this outcome, a one-level rated down score ws assumed for this criteria (-1); [b]: The sample sizes were not justified by sample sized calculation, score was rated down by one level (-1); [c]: studies achieved by the same research group and likely based on the same participants, score was rated down by one level (-1); [d]: GRADE working Group grades of evidence: very low quality: we are very uncertain about the estimate.

ABBREVIATIONS: CV: Coefficient of Variation of force signal; MVC: Maximum Voluntary Contraction; RCT: Randomized Controlled Trial.

4. DISCUSSION

4.1. Participants

The trials mostly assessed the effects of ET in healthy older adults' muscle force control. It has been shown that the senescence process involves changes in the neuromuscular system including the impairment of feedback mechanisms (e.g. joint-position sense, touch, kinesthesis, and proprioception) which are important in the control of muscle force (Cole, 1991; Desrosiers, Hébert, Bravo, & Dutil, 1996; Skinner, Barrack, & Cook, 1984). Consequently, aging is accompanied by a reduced ability to control or grade muscle force (David E. Vaillancourt & Newell, 2003) with consequent impaired functional components. Nevertheless, studies also reported an impaired muscle force control in diseases such as diabetes mellitus (Suda et al., 2017), chronic stroke (Lodha et al., 2010) and Parkinson's Disease (D E Vaillancourt et al., 2002). Guidelines concerning these pathologies recommend specific nonpharmacological interventions (ET or rehabilitation) as part of their treatment (Ammann, Knols, Baschung, de Bie, & de Bruin, 2014; Dugan, 2016; Mak, Wong-Yu, Shen, & Chung, 2017). Accordingly, studying the contribution of these interventions in improving muscle force control of older adults with such diseases would be particularly relevant. On the other hand, determining the relationship between muscle force control and some geriatric syndromes (e.g. frailty, sarcopenia, sarcopenic obesity…) as well as investigating the contribution of ET programs in improving muscle force control in older adults with such clinical conditions could be of great relevance.

4.2. Interventions

ET programs have been widely studied and recommended in addition to pharmacological and nonpharmacological therapeutic strategies in the management of the deleterious effects of the aging process (Chodzko-Zajko et al., 2009). Although regular ET triggers responses involving various physiological systems threatened by aging, evidence established that each ET modality has beneficial effects among specific physiological functions in older adults. For instance, it has been shown that resistance and aerobic exercise programs improve different aspects of older adults' muscle oxygenation depending of their clinical status (Fiogbé, de Vassimon-Barroso, & de Medeiros Takahashi, 2017). Furthermore, it has been demonstrated that aerobic (Fleg, 2012), resistance (Yamamoto et al., 2016) and fall prevention (El-Khoury, Cassou, Charles, & Dargent-Molina, 2013) training programs improve respectively aerobic capacity, muscle strength, balance, fall risk and balance in older adult. The current review is the first study aiming to provide an overview regarding trials investigating the effects of different ET modalities on the muscle force control of older adults. In the most of the included studies, participants underwent resistance training but also steadiness, and functional training programs (see Table 1 for more details about each ET modalities parameters). It should be emphasized that the greatest challenge of ET as therapeutic strategy in the management of aging is the low adherence and high dropout rates (Horne & Tierney, 2012; Picorelli, Pereira, Pereira, Felício, & Sherrington, 2014), mainly due to age-associated diseases and clinical conditions (e.g., osteoarticular, rheumatological and cardiorespiratory diseases). This hinder to carry out exercise therapies through preset strategies, thus, requiring that ET modalities are adapted to older adults' clinical specificities. Therefore, investigating the response of older adults' muscle force control to others ET modalities (e.g. multicomponent, fall prevention, water ET…) could be particularly relevant.

4.3. Experimental set-up

The trials of the current systematic review assessed muscle force control throughout various experimental set-ups with some similar aspects. For instance, except for one study (Hortobágyi et al., 2001), after measuring the individual isometric MVC, the participants were required to exert isometric contractions at different force targets calculated as percentage of the MVC, in random order, with at least 60 s of rest between trials. In contrast, the current study highlights a heterogeneity regarding various parameters of the studies' experimental set-up. First, there was a multiplicity of devices used for the assessment of muscle force control. For instance, for the knee extensor muscle's force control, some trials used isokinetic dynamometers (Hortobágyi et al., 2001; Manini et al., 2005; Tracy et al., 2004), while other studies used a load cell connected to a strain-gauge amplifier in series with a data acquisition system (Kobayashi et al., 2014; Tracy & Enoka, 2006). Afterwards, depending on studies, participants were positioned following different joints angle although assessing the same muscle. Thus, for the knee extensor muscle, Kobayashi et al., (2012) and Manini et al., (2004) positioned their participants at 95° and 60° of knee flexion (full extension = 180°) respectively. Furthermore, although the mostly of the trials calculated the force targets as percentage of the MVC, such percentage differed greatly between studies. Finally, the contractions time were also substantially different between studies assessing the same muscle. For instance, although assessing the knee extensor muscle, participants were required to sustain contractions at the target force for 5 seconds (Hortobágyi et al., 2001) or 15 seconds (Manini et al., 2005). It has been demonstrated that joints angle (Sosnoff, Voudrie, & Ebersole, 2009), force targets (Slifkin & Newell, 1999) and contractions time (Singh, Arampatzis, Duda, Heller, & Taylor, 2010) influence the muscle force control outcomes. Therefore, such heterogeneity, regarding the experimental set-up of the trials is likely a factor contributing to the contrasting findings reported in the literature.

4.4. Data analysis parameters

This systematic review highlights the lack of agreement about signal acquisition and processing choices leading to a multiplicity of data analysis parameters throughout studies. For instance, although all the included studies analyzed the steadiest window from the central region of the force signals, the length of such window as well as the sampling frequency vary greatly between studies. Accordingly, the total data points analyzed from the force signals differed throughout trials. Forrest et al, (2014) demonstrated that the choices regarding signal acquisition (e.g. sampling frequency) and processing (e.g. total data points) have a determinant impact on the value of a force complexity variable (ApEn) (Forrest, Challis, & Winter, 2014). Although no similar investigation has been conducted with SD and CV, it could be suggested that the heterogeneity regarding the data analysis parameters would be a confounding factor for the value of the muscle force control variables. Mostly, the trials investigated the muscle force control through force variability metrics (SD and CV). Only one trial assessed the frequency domain of the force signals of knee extensors with FFT analysis (Kobayashi et al., 2014) while no trial study the force complexity variables. It is widely shown that the force complexity metrics provide an insight into the dimensions of feedback control loops governing force output and the underlying state of the neuromotor system (Mayer-Kress et al., 2003), which cannot be inferred from force variability metrics. Thus, investigating the contribution of ET programs on muscle force control through force complexity metrics in addition to force variability metrics would be particularly relevant as this would provide a better understanding of the exercise-related adaptations in older adults' neuromuscular system.

4.5. Effects of exercise training

The findings showed that regardless the participants' clinical status, assessed muscles, experimental set-up, and exercise modalities, the ET programs increased the MVC (with large effect sizes), in older adults. This confirms the widely evidenced improved muscle strength after ET in older adults. The neuro-physiologically mediated mechanisms involved in such response have been widely evidenced (R M Enoka, 1997; Moritani & DeVries, 1979; SALE, 1988). Briefly, ET triggered adaptive changes within the neuromuscular system that allow to better and fully activate motor units in specific movements and to better coordinate the activation of all relevant muscles, thus effecting a greater net force in the intended direction of movement.

The production and maintenance of voluntary muscle contractions are regulated by the interaction between multiple mechanisms (i.e., feedback loops, motor unit recruitment, motor unit firing rates, and attentional control) (David E Vaillancourt et al., 2002). Accordingly, the force or displacement produced during a voluntary muscle contraction is always subject to unintentional fluctuations. Such fluctuations, known as physiological tremor don't disturb the control of muscle activities in healthy individuals (Herbert, 2012). With advancing age, there is a degeneration of motor units (Brown, 1972; Campbell, McComas, & Petito, 1973) that involves the progressive death of α-motoneurons and the reinnervation of some of the denervated muscle fibers by surviving motor units (Oda, 1984; Stålberg & Fawcett, 1982). This reorganization triggers changes in the proprieties of the motor units. Since the control of muscle force depends on the integrity of the motor units' proprieties, these changes exaggerate tremor in older adults and consequently impair their ability to produce muscle force steadily, accurately, and temporally matched to the demands of particular movement tasks. Therefore, the ability to execute precise motor tasks common to daily living, such as handwriting, object manipulation, self-lifting and postural balance may be affected in older adults. Increasingly, there is evidence that neural adaptations associated with ET programs could contribute to slow down or even reverse the age-related loss of muscle control. Indeed, the exercise-related enhanced capacity to produce force at the level of motor units implies that fewer motoneurons need to be recruited, with a consequent reduced level of cortical activation required to produce an equivalent kinetic or kinematic outcome (Dettmers et al., 1996). Furthermore, Milner-Brown et al. (1975) provided specific evidence that resistance training has the potential to increase the tendency of motor units to fire synchronously (motor unit short term synchronization) as they found that the motor units of resistance-trained individuals fired with greater synchrony than those of untrained individuals (Milner-Brown, Stein, & Lee, 1975). It has been demonstrated that such motor unit short term synchronization occurs when motoneurons receive input from axonal branches of the same presynaptic neurons, thereby increasing the probability of near-simultaneous discharge in the target motoneurons (Datta, Farmer, & Stephens, 1991; Kirkwood & Sears, 1978).

Summarily, the available evidence supports the hypothesis that ET triggered neural adaptations that contribute to improve muscle control in older adults. Unexpectedly, in the present review, the force variability variables exhibited contrasting findings in response to ET programs. While ET programs decreased the CV with negative effects size regardless the exercise modalities, assessed muscles and force targets, the response of the SD to ET varied greatly from negative to positive effects size across studies depending on force targets and exercise modalities. It should be emphasized that, negative effects size mean that the ET program contributed to decrease the studied outcome. In the context of the present study, the exercise-related decrease of the CV means an improved ability to control muscle force as response to the ET program, suggesting a beneficial adaptation of the participants' neuromuscular system to exercise. In contrast, when the muscle force control is quantified through the SD, the findings suggest both beneficial (negative effect sizes) and harmful (positive effect sizes) effects of the ET program on the older adults' neuromuscular system depending on force targets and exercise modalities. These contrasting findings are unlikely to be due to heterogeneity regarding the experimental set-up (force targets) and ET modalities since within studies, the results exhibited after ET programs differed substantially between SD and CV at several force targets. For instance, the findings of Tracy et al. (2003) showed that there was increased SD (positive effect sizes) but decreased CV (negative effect sizes) after both steadiness and strength training (See Table 3). However, such contrasting findings raise the interesting question of the difference between the calculation method of these two variables. The SD evaluate the absolute variability of the force fluctuations by merely computing the within standard deviation of the force signal whereas the CV provides a measure of the relative variability by normalizing the within standard deviation of the force signal with the mean of force output. Thus, by assessing the variability of the force signal in older adults, unlike the SD, the CV take into account the relative contribution of the individual muscle strength in the force control. It can be inferred that the differences in muscle strength between individual and studies as well as their relative influence in the force control outcomes are more minimized when analyzed through the CV of the force signal. Accordingly, the CV of the force signal likely allows more accurate values that better reflect the magnitude of fluctuations in force output.

The findings show that, in older adults, the quality of the body of evidence for the contribution of resistance training programs on the muscle force control was low for knee extensor muscle and very low for dorsal interosseus muscles.

In line with Furlan et al (2009), the findings show that there is a limited confidence about the enhancement of knee extensor muscle force control in response to resistance training programs (Furlan, Pennick, Bombardier, van Tulder, & Editorial Board, 2009). This means that future studies are likely to have a major impact on the confidence in such effect estimate. On the other hand, the findings show that, the confidence in the enhancement of dorsal interosseus muscles force control in response to resistance training programs estimation is very limited. Thus, any estimation of such effect is uncertain.

4.6. Limitations

This study has some limitations. First, it should be highlighted that the heterogeneity regarding experimental set-up and data analysis parameters between studies hindered to perform a meta-analysis, but also reduced the number of studies included in the assessment of the quality of the evidence. Consequently, the reasons for downgrading the quality of the body of evidence are mainly related to the reduced number of studies. Thereby, the current levels of evidence are likely to be influenced by further researches. Afterwards, the included studies investigated only healthy and functionally limited older adults submitted to resistance, steadiness and functional training programs. Accordingly, the current findings cannot be extrapolated to older adults with other clinical conditions and undergoing other ET modalities. Furthermore, the assessment of the method quality of the trials emphasized that no study performed secret allocation and participants, therapist and assessor blinding. Thus, it would be relevant that further investigations with higher methodological quality study the effects of different ET modalities and their combinations (multicomponent training) on muscle force control in older adults with other diseases or clinical conditions.

5. CONCLUSION

This is the first study to investigate the effectiveness of ET programs designed to improve muscle force control in older adults. Although the heterogeneity regarding experimental set-up and data analysis parameters between studies, the findings suggested that resistance, steadiness and functional training programs improve muscle force control in healthy and functionally limited older adults. However, the quality of evidence of the published clinical trials showed that the confidence about such an effect is limited the knee extensor muscle force control enhancement and very limited for dorsal interosseus muscles force control enhancement in response to resistance training programs. Therefore, further investigations with higher methodological quality are needed to quantify the effects of different ET modalities on muscle force control of older adults with different diseases or clinical conditions.

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ESTUDO III

(Versão em inglês apresentada nas normas da revista)

EFFECTIVENESS OF A MULTICOMPONENT TRAINING ON MUSCLE FORCE CONTROL IN PRE-FRAIL OLDER ADULTS: A BLINDED RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

This investigation aimed to determine the effectiveness of the Multicomponent Training Intervention (MulTI) at improving the functional capacity and muscle force control outcomes in pre-frail older adults. Twenty-eight pre-frail older adults were randomly divided into a trained group (n=16), submitted to the MulTI (combining aerobic, balance and strength exercises), and a control group (n=12). The measurements included knee extensors' maximal (MVC) and submaximal voluntary contractions (SIC, targeted at 15, and 40% of MVC), and the usual 4.6-m gait speed test (GST). The force control was assessed by calculating the variability (coefficient of variation, CV) and complexity (sample entropy, SampEn) of the SIC torque data. The MulTI resulted in an increased in an increased torque complexity and GST but no significant improvements in knee extensor MVC force and torque variability. This is the first study to demonstrate the effectiveness of multicomponent exercise program in improving muscle force control and functional capacity in pre-frail older adults.

KEYWORDS

Frailty, Multi-domain exercise, Knee extensor strength, entropy, functional capacity.

INTRODUCTION

Due to the worldwide rapid increase of the older adult's population, healthcare systems are facing new challenges related to increasingly prevalent geriatric syndromes and chronic diseases that require more specific therapeutic strategies (1). Frailty is currently considered as one of the most prevalent geriatric syndromes (2) and is characterized by decreases in the biological functional reserve and resistance to stressors due to changes in several physiological systems (3). This syndrome leads to a clinical condition that encompasses adverse outcomes such as falls, hospitalization, disability, death, and increased risk of functional decline (3).

The main pathophysiological issues underlying functional impairments in older adults are thought to be related to age-induced changes in the neuromuscular system including loss of skeletal muscle mass and force as well as fat infiltration (4). Accordingly, the impaired functional capacity, observed in the main geriatric syndrome such as frailty, are often investigated throught functional outcomes and muscle maximal force measurements (5). However, despite its accessibility and although being a key criterion for the diagnosis of this syndrome, muscle maximal force measurements fail to yield an insight into the neurophysiologically mediated mechanisms underlying the decline in physical performance observed in frailty. Rather, it has been suggested that, in older adults, the declines in functional capacities are more closely a matter of an impaired ability to control muscle force than a decreased capacity to generate maximal force (6).

The force produced during a voluntary muscle contraction is always subject to unintentional fluctuations, known as physiological tremor (7). The analysis of these fluctuations during standardized tasks become a increasingly used method to assess the muscle force control. Unlikely the muscle maximal force measurement, muscle force control metrics yield a better comprehension of the neuromuscular system underlying state, providing insights into mechanisms governing force output (8). Routinely, studies investigate the muscle force control throught the statistical metrics (e.g. coefficient of variation; CV) (9). Higher values mean higher force variability that is a poor muscle force control. However, as consequent of the interactions between the components of the neuromuscular system, the force output fluctuates according to an irregular, non-linear and chaotic (complex) behavior whose temporal structure can’t be analyzed through classic statistical metrics (10). Therefore, it has been proposed to analyze the force fluctuations complexity using methods derived from non-linear dynamics such as sample entropy (SampEn) (11). Higher entropy metrics’ values mean greater complexity of force output that is a better muscle force control. This implies an optimal ability to rapidly and accurately adapt muscle force in response to any internal or external needs or demands. Decreased force complexity has been evidenced in older adults (12) and in diseases such as chronic stroke (13). Although Lipsitz postulated that frailty is characterized by a loss of physiological complexity (14), this hypothesis has not been tested in the neuromuscular system since there is no study aiming to investigate force complexity in pre-frail or frail older adults.

Evidence demonstrated that frailty is more reversible at early stages (15). Therefore, examining the effectiveness of interventions aiming to prevent or treat functional declines and disability in older adults at frailty early stage is gaining interest (16). The effectiveness of exercise programs in frail older adults have been the focus of considerable trials (17,18) and sytematic reviews (19,20). Mostly, the authors demonstrated the superior nature of multicomponent exercise programs (i.e. exercise programs including strength, endurance, balance/gait and flexibility components) as opposed to single component exercise programs. However, of this large number of studies (17,18,20), only a small part focused on older adults at frailty early stage (19).

Summarily, i) frailty has been shown to be related to loss of physiological complexity (14) and impaired functional capacity (3), ii) this syndrome is more reversible at its early stages (15), and iii) multicomponent exercise programs have been suggested to present better results than single component exercise programs (19,20). Therefore, this investigation aimed to determine the effectiveness of the Multicomponent Training Intervention (MulTI) at improving the functional capacity and muscle force control outcomes in pre-frail older adults. The hypothesis was that the proposed training protocol could improve functional capacity and muscle force control outcomes in this population.

METHODS

Study design and subjects

This was a blinded randomized controlled trial, approved by the Research Ethics Committee and registered in clinicaltrials.gov, a clinical trial web-based resource. All participants were informed about the experimental procedures and signed a formal acceptance form.

The sample size calculation was performed through the G*Power program, and suggested that a sample containing 28 participants would carry a power of 80%, with an effect size of 0.25 and alpha of 0.05. One hundred and sixty-seven subjects aged 65 years old or older were screened for frailty using the phenotype of Fried et al. (2001) (3). The criteria were: i) reduced handgrip strength, ii) reduced gait speed, iii) unintentional weight loss, iv) self-reported exhaustion as identified by two questions (questions 7 and 20) from a depression scale from the Center for Epidemiologic Studies (21) and v) low physical activity level, according to the Minnesota Leisure Time Activity Questionnaire (22).

Participants who were positive for 1 or 2 criteria were considered pre-frail. Seventy-seven of the screened subjects were classified as pre-frail and invited to a formal assessment to verify compliance with the criteria. To be include, participants were required to: have a medical release for exercise from a cardiologist associated to the study, understand instructions, have preserved walking capacity, (the use of assistive devices was allowed, except a wheelchair), not present stroke history; cognitive deficit (Mini Mental State Examination score lower than 18), visual self-reported disorders and lower limbs previous surgery.

Forty of the assessed subjects met the inclusion criteria and were included in the study. These participants underwent the study's baseline assessments. Afterward, they were randomly distributed into blocks of eight subjects by a separate researcher who were blinded about the allocation of the participants. After this process, the participants were divided in control (n=20) or MulTI (n=20) group. The participants who dropped out the MulTI sessions or did not perform the assessments after the study period were excluded from the study analyses. Figure 1 presents the flowchart of the study.

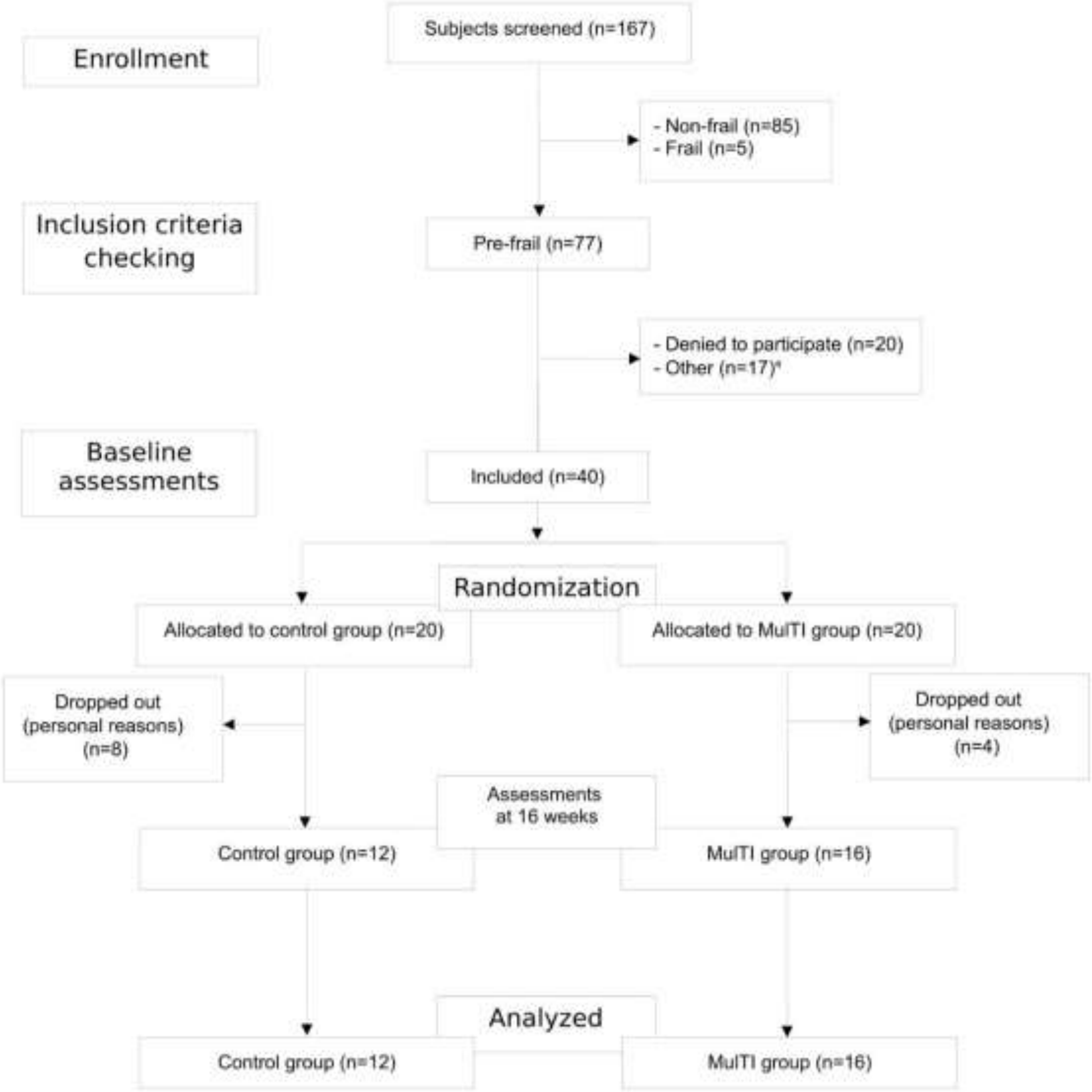

Figure 1. Flowchart of the study.

[a](withdrawn after medical evaluation, n=5; cognitive déficit, n=5; stroke history, n=2; visual self-reported disorders, n=1; incomplete screening, n=4).

Experimental design

The study was blinded regarding participants allocation (JHA), training conduction (ACSMF and BFC) and data analysis (E.F), thereby the randomization process, MulTI application and analysis of results were performed by different research teams. Only the MulTI group underwent the exercise program while the control group were instructed not to interrupt any type of exercise, they may already practice. After the study period, the control group was invited to participate to an identical MulTI for at the least the same training period. All participants were assessed at baseline (week 0) and after the intervention (week 16). The measurements included knee extensors' maximal voluntary contractions (MVC) and force control assessments as well as the 4.6-m gait speed test (GST). Participants were required to visit the laboratory on the day before the experiment to familiarize themselves with the procedures and equipment to be used. They were instructed to avoid caffeinated and alcoholic beverages and moderate-to-heavy exercise in the 24 hours preceding the protocol. They were interviewed on the day of the experiment to confirm their health condition and the occurrence of a regular night sleep. All subjects were evaluated at the same time of the day.

Experimental setup

Knee extensors MVC force

The MVC of the dominant leg knee extension was tested at 60° of knee flexion (full extension = 0°) using an isokinetic dynamometer (Biodex Multi-Joint System III, Biodex Medical System Inc., Shirley, NY, USA). The load cell was calibrated before each test by positioning and stabilizing the lever arm parallel to the floor and by hanging a known weight on the load cell. Subjects were positioned on the dynamometer chair (seat back angle = 90°) and were stabilized by using pelvis, chest, and thigh straps. Participants performed 3 isometric

MVC for 10 seconds with a 5-min resting period between each contraction. During the MVC, participants were motivated with loud and consistent verbal encouragement and were instructed to avoid contracting other muscles, and to keep breathing spontaneously. The highest of the three MVCs was used as the peak torque (PT) value.

Muscle force control assessment

The muscle force control was assessed by analyzing the torque output signal recorded during submaximal isometric contractions of the dominant-leg knee extensors. Participants performed two single-repetition submaximal isometric contractions (SIC) of the dominant-leg knee extensors at 15% and 40% of the predetermined PT, in a random order. The contractions were maintained for 30 s with a 5-min resting period between each contraction.

The data acquisition and analysis parameters are described by Fiogbé et al. (2018) (12). Briefly, data were acquired from an isokinetic dynamometer (Biodex Multi-Joint System III, Biodex Medical System Inc.), which collected the torque output signal at a sampling rate of 100 Hz. All metrics of variability and complexity were calculated using the SIC data. To eliminate the transient effects of the initial isometric torque adjustments and early termination, the first 7 s and final 1 s of torque samples from each contraction were removed. The steadiest 3 s from the remaining torque samples were used for subsequent analysis. The torque variability of each contraction was measured using the coefficient of variation (CV). The temporal structure of the torque fluctuations (i.e., the torque complexity) was examined using the SampEn. The input parameters for the calculation of SampEn were an embedding dimension (m) of 2, a tolerance (r) of 0.2, and a sample size (n) of 300. Further details regarding the estimation procedures are described by Porta et al. (2007) (23).

Gait speed test

The time required to walk a 4.6-m distance at usual pace was recorded three times with a stopwatch by a previously trained physical therapist. The total test was performed over a route of 8.6 m over a smooth walking surface with no obstacles. To eliminate the effect of acceleration and deceleration of gait, the 2 m at the beginning and end of the route were disregarded for the calculation of walking speed. The GST was calculated by dividing the walking distance (4.6 meters) by the mean time (in seconds) of the three attempts. After the study period, gait speed increments greater or equal to 0.1 m/s were defined as clinically significant for meaning an enhanced functional capacity and increased survival (24).

Training protocol

The MulTI was designed following the recommendations of the American College of Sports Medicine (ACSM) (25) combining aerobic, muscle strength, flexibility, and balance exercises. The protocol consisted of three weekly 60-minute sessions for 16 weeks according to the structure presented in Table 1.

Table 1. Structure of the Multicomponent Training Intervention (MulTI)

Training Component	**Exercise**	**Intensity**	**Progression**
Warm-up (10 minutes)	Light walk	Free and spontaneous intensity	Increased progressively until reaching the aerobic component intensity.
Aerobic exercises (20 minutes)	Walking on the ground or on the treadmill	Intensity of the exercises will correspond to a training heart rate (THR) calculated from the resting HR with an increase of 45-80% of the heart rate reserve (HRR).	The training will start at 45% HRR in the first two weeks and will increase by 5% every two weeks until reaching 80% HRR(26). During the training sessions, the THR will be monitored using heart rate monitors (Polar Electro Co. Ltda. Kempele, Finland).
Balance exercises (10 minutes)	Walk in tandem or in circles, training of balance and ankle, hip, and step strategies.	If necessary, a physiotherapist will manually induce a slight unbalance.	The progression of these exercises will be performed in relation to the support base, in the following order; bipodal, semi-tandem, and tandem associated with visual disturbance (visual conflict glasses, closed eyes), different surfaces (rigid and foam) (25), changes in the direction and speed, and overload of muscular groups involved in the posture (walking on tiptoe, heel).
Muscular strengthening (15 minutes)	Sit to stand from the chair; proprioceptive neuromuscular strengthening for the upper limbs, on the principal and secondary diagonals; calf exercises; lunges; step up and step down, alternating the order of stepping between the lower limbs.	One set of 8-12 repetitions at the resistance training load initially determined	The resistance training load will be adopted following the same criterion of progression mentioned in the familiarization (through the Borg CR-10 Scale).(20)
Warm-down (5 minutes)	Breathing exercises and overall stretching.	30-60s of static stretching(25)	Until reaching resting HR and BP

Sessions were held collectively with groups of 4 participants per session; however, exercise intensity prescription and patient monitoring were carried out individually. Before the start of each session, measurements of the resting blood pressure and HR were collected. In the week before the beginning of training, three sessions were performed with a 48-hour interval between each session, in order to familiarize the participants with the exercises and determine the resistance training load. The resistance training exercises are represented in Figure 2. For each exercise, the participants performed one set of 8 repetitions without additional weight and were required to report the level of effort according to the Borg CR-10 scale (27). Next, participants were asked about the rate of effort of the muscles involved in the exercise. If this score was between 5 and 8 on the Borg CR-10 scale, the repetitions as well as the load were maintained for the first two weeks of resistance training. If below 5, the number of repetitions was progressively increased to 12. If the volunteer reported a score below 5, even after performing 12 repetitions, a 0.5-kg load was added to the involved limb, segment or to the waistcoat designed for this purpose (see figure 2) (20).

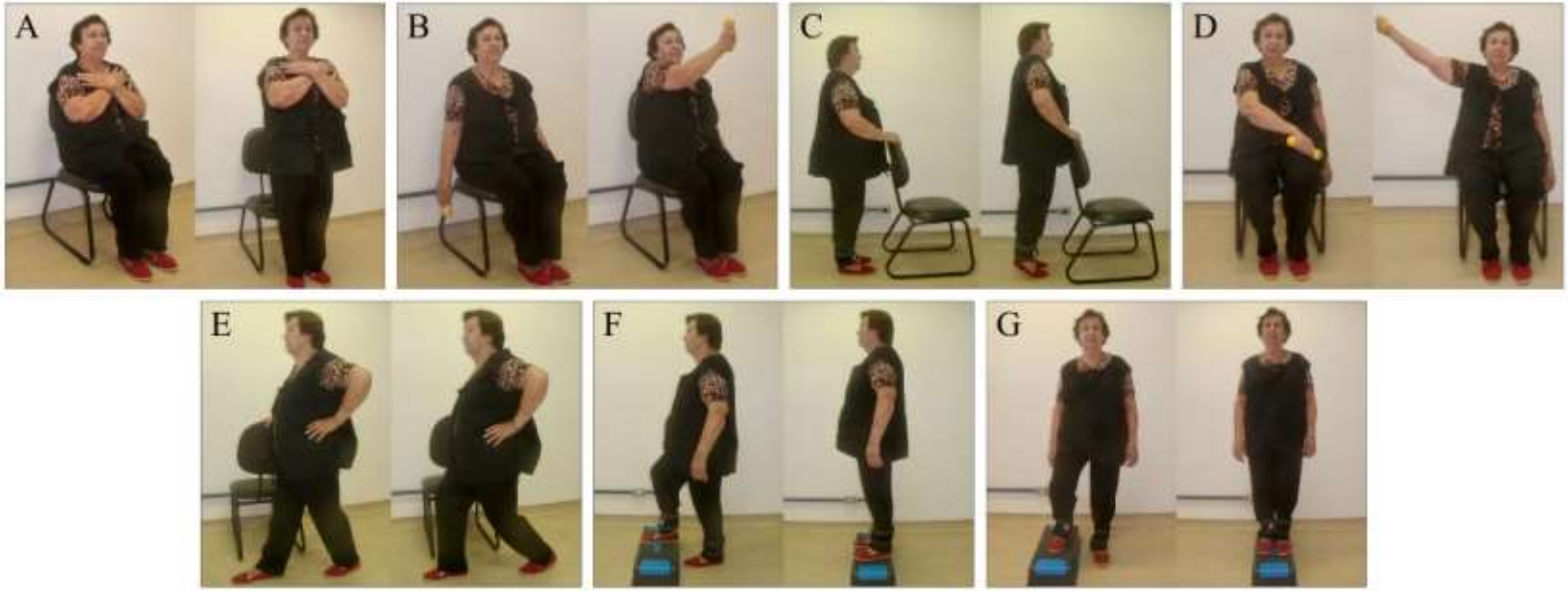

Figure 2. Illustration of exercise; A: Sit to stand from the chair, B & D: Strengthening exercise for the upper limbs C: calf exercises, E: lunges, F: step up and step down and G: alternating the order in stepping between the lower limbs.

Statistical analyses

The differences between groups for physical characteristics of the subjects at baseline were examined by the independent-samples t-test and the the $\chi 2$-test. The two-way mixed within-between subject's analysis of variance was used to test the diferences within (Baseline vs. post 16-week) and between (Control vs. MulTI group) groups for the GST, knee extensors' MVC as well as torque variability (CV), and complexity (SampEn) metrics. The effect sizes (ES) were calculated using the partial eta squared ($\eta^2{}_p$) (28) and its 95% confidence interval. An effect greater than 0.14 was considered large, between 0.01 and 0.06 medium and less than 0.01 small (29). All statistical procedures were performed with SPSS for windows (version 17.0.1, SPSS Inc, Tokyo, Japan). Statistical significance was chosen at a level of 0.05 for all comparisons.

RESULTS

At baseline, the physical characteristics did not differ between the control ([mean±SD]: age, 73.17±6.10 years; stature, 1.56±0.07 m; body mass, 69.42±11.72 kg; body mass index, 28.6±5.6 kg/m²; female, n=8; male, n=4) and the MulTI group ([mean±SD]: age, 76.44±6.48 years; stature, 1.56±0.06 m; body mass, 76.17±11.34 kg; body mass index, 31.58±4.94 kg/m²; female, n=12; male, n=4).

The comparison of the performance at the GST, knee extensors' peak torque values' as well as torque variability (CV) and complexity (SampEn) metrics between groups, at baseline and after the study period, are presented in Table 2.

The GST showed no significant group-by-time interaction (p= 0.08) and no effect of group (p= 0.46). However, there was a significant effect of time (p= 0.004). Therefore the gait speed increased after the study period regardless of group. Although being statistically no significant, the average increment of the gait speed was clinically significant in the MulTI group ([mean±SD]: 0.15±0.18 m/s), but not in the control group ([mean±SD]: 0.04±0.12 m/s). Furthermore, fourteen participants (87.5%) in the MulTI showed a gait speed increment greater or equal to 0.1 m/s, while this was observed in only five participants (41.67%) in the control group. The ES shown that the MulTI had a medium effect (η^2_p=0.11) on the participants usual gait speed.

Statistical analysis of the knee extensors' peak torque revealed that there was no significant group-by-time interaction (p= 0.09) and no effect of group (p= 0.61) or time (p= 0.47). The ES revealed a medium effect (η^2_p=0.11) of the MulTI on the participants' knee extensors' peak torque.

At both force levels, the CV showed no significant group-by-time interaction (p=0.66 and p=0.36 respectively at 15% and 40% MVC) and no effect of group (p=0.66 and p=0.38 respectively at 15% and 40% MVC) or time (p=0.09 and p=0.74 respectively at 15% and 40% MVC). Moreover, the MulTI promoted a small (η^2_p=0.00) and medium effect (η^2_p=0.05) on participants' CV, respectively at 15% and 40% MVC. At 15% MVC, the SampEn showed a significant group-by-time interaction (p= 0.02), as well as a significant effect of group (p= 0.02) and time (p< 0.001). At baseline, the values SampEn at 15% MVC were not statistically diferent between groups (p= 0.22). After 16 weeks, the values of SampEn at 15% MVC remained unchanged in the control group (p= 0.17) while it increased in the MulTI group (p< 0.001). After the study period, the MulTI group exhibited higher values than the control group (p= 0.002). The ES suggested a large effect (η^2_p=0.18) of the MulTI on the participants' SampEn at 15% MVC. At 40% MVC, the SampEn showed a significant group-by-time interaction (p< 0.001) but no group (p= 0.45) or time (p= 0.06) effect. At baseline, the values SampEn at 40% MVC were not significantly diferent between groups (p= 0.35). After 16 weeks, SampEn at 40% MVC decreased in the control group (p= 0.04) while it increased in the MulTI group (p< 0.001).

Furthermore, after the study period, the MulTI group exhibited higher values than the control group ($p= 0.02$). The ES suggested a large effect ($\eta^2_p=0.58$) of the MulTI on the SampEn at 40% MVC.

Table 2. Gait Speed Test, knee extensors's peak torque and force control variables at baseline and after the study period

	Control		MulTI		Effect size [95% CI]
	Baseline	Post 16-week	Baseline	Post 16-week	
Gait Speed Test (m/s)	0.94±0.20	0.97±0.23	0.82±0.26	0.97±0.19	0.11 [0.00, 0.35]
Peak Torque (N.m)	110.73±47.97	100.00±31.04	111.25±39.89	115.69±43.38	0.11 [0.00, 0.34]
Force control variables					
15% MVC					
Coefficient of variation	1.35±0.51	1.43±0.45	1.42±0.63	1.51±0.72	0.00 [0.00, 0.01]
SampEn	0.60±0.19	0.68±0.18	0.70±0.27	0.96±0.23*†	0.18 [0.00, 0.42]
40% MVC					
Coefficient of variation	1.17±0.57	1.36±36	1.50±0.74	1.43±0.59	0.05 [0.00, 0.26]
SampEn	0.88±0.24	0.80±0.20*	0.84±0.26	1.04±0.24*†	0.58 [0.30, 0.72]

Notes. MulTI: Multicomponent Training Intervention group, MVC: isometric maximum voluntary contraction, SampEn: Sample Entropy. CI: Confidence Interval, *P<0.05: Baseline vs Post 16-week, †P<0.05: Control vs MulTI.

DISCUSSION

The main findings of this investigation was that, the 16-week MulTI resulted in an increased knee extensor torque complexity and gait speed but no significant improvements in knee extensor MVC force and torque variability.

Routinely, the effectiveness of exercise training on older adults' muscle force control has been investigated by assessing force variability metrics in healthy individuals undergoing single component training programs (30,31). This study adresses some bias and limitations inherent to a such approach by examining the effectiveness of a multicomponent exercice program on the knee extensors' torque complexity in pre-frail older adults. This seems to be particularly relevant for two reasons ; i) frailty is currently recognized as one of the most prevalent geriatric syndromes (2) characterized by a loss of physiological complexity (14), while ii) multicomponent training programs have been suggested to be more effective than single component exercise programs (19,20) in promoting beneficial changes in older adults.

The findings show that the MulTI was effective to enhance the knee extensors' torque complexity in pre-frail older adults. Unfortunately, the only study aiming to investigate the effects of an exercise program on older adults' force complexity restricted the musculature to the hands and wrists (32). Authors concluded that a 6-week strength exercise program increased force complexity during finger-pinch tasks. The measures of force complexity provide an insight into the dimensions of feedback control loops governing force output and the underlying state of the neuromotor system (33), which cannot be inferred from force variability metrics. The neurophysiologically mediated mechanisms underlying exercise-induced force complexity improvement in pre-frail older adults are far to be unveiled. However, it has been suggested that force complexity enhancements are related to changes in the regulatory mechanisms of the neuromuscular system that shift from fewer, stronger, and more dominating neural oscillators operating across fewer time scales to multiple and equally operating neural oscillators operating across multiple time scales (34). In other words, the exercise training leads to an increase of the adaptive flexibility to coordinate the excitatory and inhibitory properties of the neural oscillators that input to the motor neuron pool. Thus, the trained participants are more able to regulate each of these neural oscillators in a coordinative output to match the required task demand (35). Consequently, they increased the number of force production modes available and hence, the adaptability and flexibility in precisely controlling mucle forces (36).

On the other hand, after 16 weeks, the control group exhibited a decreased torque complexity at moderate force target. Although Lipsitz postulated that frailty is characterized by a loss of physiological complexity (14), this is the first clinical trial extending this hypothesis to the neuromuscular system. The exact mechanisms underlying the loss of muscle force complexity in the frailty syndrome remains poorly investigated. However, it is known that the age-related loss of force complexity is due to ischemic loss of neuronal tissue, alpha motor neurons, and motor units (37), decreased modulation of the descending drive (38) as well as altered discharge rates and recruitment/derecruitment potentials of individual and populations of motor units (39). This results in fewer attractors, reduced number of control processes, and/or decoupling of control processes (40). This leads to more structured force output, relatively fixed or stereotypic patterns in motor coordination (41).

Unexpectedly, the 16-week MulTI fails to enhance knee extensor MVC force and torque variability. These findings are consistent with previous evidence that reported that exercice training triggered no change in muscle maximal force (18,42) and force fluctuations (i.e. force variability) during isometric contractions (43,44) in older adults. The exercise-induced changes in force variability have been attributed to the improved capacity to generate muscle maximal force (45). Indeed, at the motor units' level, this implies that, there is a reduction of the number of motoneurons needed to produce the same level of force. Accordingly, there is a reduced level of cortical activation required to produce an equivalent kinetic or kinematic outcome (45). On the other hand, there is evidence suggesting that the effects of exercise training on muscle maximal strength are optimized when combined with nutritional intervention (46). Although the exact mechanisms underlying frailty process are far to be fully unveiled, chronic undernutrition (i.e. inadequate intake of protein and energy, and micronutrient deficiencies) has been clearly reported to be a key contributor of multiple musculoskeletal changes that play a main etiologic role in the frailty process (3). Although the present study did not include nutritional assessment, it may be hypothesized that, the combination of the MulTI with a nutritional intervention would optimize the exercise-related gain of the muscle maximal strength in pre-frail older adults. This would likely leads to significant improvement in the knee extensors' force variability.

The findings showed that the MulTI promoted a clinically significant increment of the participants gait speed as the most of the trained participants exhibited a gait speed increment greater to 0.1 m/s. The efficiency of multicomponent exercise programs in improving the gait speed of pre-frail older adults has been demonstrated in previous clinical trials (47). Epidemiological cohort studies demonstrated that the usual gait speed is associated with survival among older adults (48,49) and reflect their functional status (50). Furthermore, after analyzing data from 9 cohort studies, Studenski et al, concluded that older adults' survival increased across the full range of gait speeds, with significant increments per 0.1 m/s (24). Accordingly, the current findings suggest an adaptation of great importance for these subjects. The exact mechanisms underlying this improvement in pre-frail older adults are not fully demonstrated. However, previous studies suggested that slowing gait in older adults may reflect both damaged systems (51) and high energy cost of walking (52). Moreover, decreasing mobility may induce a vicious cycle of reduced physical activity and deconditioning that has a direct effect on health and survival (48). Therefore, it could be hipothesized that the MulTI promoted adaptations in multiple organ systems leading to an increased survival in these participants.

This study has some limitations. First, the muscle force control indices were calculated using isometric torque signals rather than dynamic ones. Indeed, evidence demonstrated that the entropy measures (that provide better insights into mechanisms governing force control) fail to estimate the complexity of non-stationary biological signals (53), as are dynamic torque signals. Nevertheless, since the investigated functional capacity tests are dynamic task, it should be assumed that any interpretation from links between functional capacity outcomes and muscle force control indices implies some uncertainty. Afterward, a nutritional assessment would yield a better distinction between exercise and nutritional-related changes in muscle maximal force after the study period. Furthermore, besides the torque output measurements, records and analyses of the electromyographic activities would provide a better understanding of the behavior of neural properties such as motor unit recruitment, firing rate.

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CONSIDERAÇÕES FINAIS E DESDOBRAMENTOS FUTUROS

Os estudos realizados contribuíram com informações importantes a respeito de aspectos ainda incipientes no estudo do controle da força muscular em idosos.

O **Estudo I** foi o primeiro a examinar a teoria da reduzida complexidade fisiológica com o envelhecimento no sistema neuromuscular, em grandes músculos posturais. Os resultados desse estudo mostraram que embora a complexidade do torque dos extensores do joelho esteja reduzida nos indivíduos idosos, sua relação com a intensidade de contração isométrica é similar com a dos sujeitos jovens. Isso sugere que apesar da diminuição das interações entre os componentes do sistema neuromuscular, devido à idade, a organização do controle da força muscular permanece preservada em idosos.

O **Estudo II**, por sua vez, mostrou que o treinamento físico tem um efeito benéfico sobre o controle da força muscular de idosos. No entanto, tal resultado está baseado em investigações avaliando os efeitos de programas de treinamento de componente único sobre índices da variabilidade da força de indivíduos saudáveis. Dessa forma, esse estudo mostrou a necessidade de elaborar estudos abordando os principais limites metodológicos ressaltados na literatura disponível.

O **Estudo III** demonstrou que o programa de exercícios multicomponentes promoveu melhorias no controle da força muscular mas não teve efeitos sobre a força muscular e capacidade funcional de idosos pré-frágeis. Além disso, os achados sugeriram que, nessa população, as melhorias na capacidade funcional, em resposta ao exercício físico, são relacionadas às melhorias na capacidade de controlar a força muscular. Esses resultados têm uma grande relevância clínica, apresentando o programa de exercícios multicomponentes como ferramenta terapêutica eficiente no tratamento de idosos pré-frágeis. Dessa forma, através de um programa de treinamento simples e de baixo custo, é possível melhorar o controle da força muscular, prevenindo assim prováveis decréscimos da capacidade funcional devido à síndrome da fragilidade.

Como desdobramentos futuros do presente estudo, três estudos foram planejados. O primeiro terá como objetivo de avaliar a contribuição relativa da sarcopenia no controle motor e na capacidade funcional de idosos pré-frágeis. O segundo examinará as alterações de componentes neurais, subjacentes à perda do controle motor em idosos pré-frágeis, por meio da análise do sinal eletromiográfico. O terceiro estudo terá como objetivo determinar a cronologia das adapatações neuromusculares em resposta ao programa de treinamento multicomponente. Por isso, idosos pré-frágeis serão submetidos a um programa de treinamento multicomponente de maior duração combinado com suplementação nutricional e avaliações intermediárias dos índices do controle da força muscular e do sinal eletromiográfico.

ATIVIDADES REALIZADAS DURANTE O DOUTORADO

Durante o período de realização do Doutorado (Outubro de 2014 a Novembro de 2018) foram desenvolvidas atividades relacionadas aos projetos de pesquisa de responsabilidade da Profa. Dra. Anielle Cristhine M. Takahashi, sendo elas:

- Elaboração de pesquisas preliminares visando a inserção da avaliação da oxigenação muscular em indivíduos idosos como parte do projeto desta tese. Problemas técnicos dificultaram o andamento destas atividades. No entanto, um artigo intitulado “Exercise training in older adults, what effects on muscle oxygenation? A systematic review” foi publicado no periódico *Archives of gerontology and geriatrics* (2017) como fruto dos estudos preliminares.
- Colaboração no projeto da aluna de mestrado Bianca Ferdin Carnavale que resultou no artigo “Complexity of knee extensor torque in patients with frailty syndrome: a cross-sectional study” publicado no periódico *Brazilian Journal of Physical Therapy* (2018).
- Participação no projeto do Laboratório de Pesquisa em Saúde do Idoso (LaPeSI) que resultou na submissão do artigo “The PF-MulTI project for complexity of biological signals, functional capacity and cognition improvement in pre-frail elderly: A blinded randomized controlled study protocol” ao periódico *Geriatrics & Gerontology International* (2018).
- Participação no projeto de extensão “Revitalização geriátrica: Novos desafios”.

Finalização das análises e elaboração do artigo: “Water exercise in coronary artery disease patients, effects on heart rate variability, and body composition: A randomized controlled trial” do mestrado, publicado no periódico *Physiotherapy Research International* (2018).

Orientação da aluna Taís Helena Fragale Baio de Especialização em Envelhecimento e Saúde da Pessoa Idosa da Universidade Federal de São Carlos, a qual desenvolveu o Trabalho de Conclusão de Curso intitulado “Nos últimos 5 anos, qual programa de treinamento físico permite melhor prevenção de queda em idosos? Uma revisão sistemática”.

Orientação da aluna Zakiyah Tchacoula em graduação em fisioterapia na Université de Abomey Calavi República do Benin, a qual desenvolveu o Trabalho de Conclusão de Curso intitulado “Étude de l’intégrité de la modulation autonome de la fréquence cardiaque du patient insuffisant cardiaque”.

Orientação do aluno Wilfred Bonou em graduação em fisioterapia na Université de Abomey Calavi República do Beni, a qual desenvolveu o Trabalho de Conclusão de Curso intitulado “La modulation autonome de la fréquence cardiaque du sujet sain et sa relation avec la température et l’humidite relative de l’air”.