UNIVERSIDADE FEDERAL DE SÃO CARLOS
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REPERCUSSÕES CARDIOVASCULARES DE UM TREINAMENTO MULTICOMPONENTE EM IDOSOS PRÉ-FRÁGEIS

MARCELE STEPHANIE DE SOUZA BUTO

São Carlos
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MARCELE STEPHANIE DE SOUZA BUTO

Tese apresentada ao Programa de Pós-Graduação em Fisioterapia da Universidade Federal de São Carlos requisito parcial para obtenção do título de Doutor em Fisioterapia. Área de concentração: Fisioterapia e Desempenho Funcional.
Orientadora: Profa. Dra. Anielle Cristhine de Medeiros Takahashi

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RESUMO

A síndrome da Fragilidade é descrita como um estado clínico de vulnerabilidade ao estresse, resultado do declínio da resiliência e de reservas fisiológicas associadas ao envelhecimento. Com a progressão da fragilidade a manutenção da homeostase é afetada, a interação entre os sistemas fisiológicos se torna debilitada e pode repercutir em comprometimento no controle cardiovascular pelo sistema nervoso autônomo (SNA). Devido à multidimensionalidade da Fragilidade, medidas de complexidade como a entropia de amostragem (SampEn) e sensibilidade barorreflexa (SBR) podem ser ferramentas mais adequadas para mensurar estas interações nas dinâmicas cardiovasculares. Para o manejo da Fragilidade, intervenções multicomponentes demonstraram-se efetivas nas funções físicas, na capacidade funcional e no status de fragilidade principalmente em estágios intermediários (pré-fragilidade). No entanto, não se sabe se também apresentaria repercussões benéficas no controle cardiovascular, bem como na restauração da complexidade da FC e da SBR. Assim, esta tese divide-se em dois estudos. O **Estudo I** intitulado "Multicomponent exercise training does not improve cardiovascular control in prefrail older adults: a blinded randomized clinical study" teve como objetivo verificar se um treinamento multicomponente de 16 semanas apresentaria efeito no controle cardiovascular de idosos pré-frágeis. Os resultados mostraram que o treinamento multicomponente não foi efetivo na melhora do controle cardiovascular, bem como no desempenho do teste de caminhada de 6 minutos de idosos pré-frágeis. O **Estudo II** intitulado "Multicomponent exercise training in cardiovascular complexity in prefrail older adults: a blinded randomized clinical study" teve como objetivo avaliar a eficácia de um treinamento multicomponente na complexidade da FC e na SBR de idosos pré-frágeis. Os resultados indicaram que não houve melhora nas dinâmicas da FC, enquanto complexidade e barorreflexo. No entanto, indivíduos que não realizaram o treinamento apresentaram uma piora (redução) da complexidade ao longo do tempo. Assim, sugere-se que houve manutenção da complexidade da FC em idosos pré-frágeis que participaram da intervenção.

Palavras-chave: Barorreflexo, complexidade, envelhecimento, exercício físico, fragilidade, sistema nervoso autônomo.

Buto, MSS. Cardiovascular repercussion of a multicomponent training in Prefrail older adults [Thesis]. São Carlos: Programa de Pós-Graduação em Fisioterapia, Universidade Federal de São Carlos; 2019.

ABSTRACT

Frailty syndrome is described as a clinical state of vulnerability to stress resulting from the decline of resilience and physiological reserves related to aging. As Frailty progresses, homeostasis maintenance become affected, as well the interactions between the physiological systems and may impair the cardiovascular control by the autonomic nervous system (ANS). Considering the multidimensionality feature of Frailty, complexity measures such as Sample entropy (SampEn) and baroreflex sensitivity (BRS) may be more adequate tools to measure these interactions in cardiovascular dynamics. For Frailty management, multicomponent interventions have been shown to be effective in physical functions, functional capacity and frailty status, mainly in intermediate stages (pre-frailty). Nonetheless, it is unclear if it would also have beneficial repercussions in cardiovascular control as well as restoring the HR complexity and BRS. Thus, this thesis is divided into two studies. The **study I** "Multicomponent exercise training does not improve cardiovascular control in prefrail older adults: a blinded randomized clinical study" aimed to verify if a multi-component training of 16 weeks would have effect in the cardiovascular control of prefrail older adults. The results showed that multicomponent training was not effective in improving cardiovascular control as well as in the performance of the 6-minute walk test of prefrail older adults. The **study II** “Multicomponent exercise training in cardiovascular complexity in prefrail older adults: a blinded randomized clinical study” aimed to evaluate the efficacy of multicomponent training in the HR complexity and BRS in prefrail older adults. The results indicated there was no improvement in the HR dynamics as complexity and baroreflex. However, individuals who did not perform the training presented a worsening (reduction) of HR complexity over time. Thus, it is suggested the maintenance of HR complexity in prefrail older adults who participated in the intervention.

Keywords: Baroreflex, complexity, aging, physical exercise, frailty, autonomic nervous system.

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LISTA DE ABREVIATURAS E SIGLAS

ANS	Autonomic Nervous System
ApEn	Approximate Entropy
ATS	American Thoracic Society
BMI	Body Mass Index
BP	Blood Pressure
BRS	Baroreflex Sensitivity
CG	Control Group
CVD	Cardiovascular Disease
DCV	Doenças cardiovasculares
ECG	Eletrocardiogram
FC	Frequência cardíaca
HF	High Frequency
HR	Heart Rate
HRR	Heart Rate Reserve
IBGE	Instituto Brasileiro de Geografia e Estatística
K^2	Coerência
LF	Low Frequency
LF/HF	Low Frequency – High Frequency ratio
MMSE	Mini Mental State Examination
MulTI	Multicomponent Training Intervention group
RRi	R-R Interval
SampEn	Sample Entropy
SBR	Sensibilidade barorreflexa
SNA	Sistema Nervoso Autonômo
THR	Training Heart Rate
VFC	Variabilidade da frequência cardíaca
$VO_{2\ max}$	Maximum Oxygen uptake
WD	Walk Distance
6MWT	6-minute walk test
α	Ganho do barorreflexo

SUMÁRIO

1. CONTEXTUALIZAÇÃO

O envelhecimento populacional é um fenômeno que vem ocorrendo de forma acelerada a nível global. Atualmente no Brasil, o percentual de pessoas com idade superior a 65 anos corresponde a 9,2% da população. As projeções estimam que em 2060 atinja 25,5% (58,2 milhões de idosos), o equivalente a um quarto da população total (IBGE, 2018). Neste importante período de transição demográfica, uma das maiores e mais emergentes implicações de saúde pública é a síndrome da Fragilidade (BOCK et al., 2016; GUSTAVSON et al., 2017).

Esta síndrome é descrita como um estado clínico de vulnerabilidade ao estresse, resultado do declínio da resiliência e de reservas fisiológicas associadas ao envelhecimento (FRIED et al., 2001). Sua prevalência no Brasil varia entre 8,0 a 22,8% (SOUSA et al., 2011; MACUCO et al., 2012; MOREIRA; LOURENÇO, 2013; VIEIRA et al., 2013) e uma combinação de fatores como idade, gênero, estilo de vida, condições socioeconômicas, comorbidades e cognição parece contribuir diretamente no desenvolvimento desta condição (ROCKWOOD et al., 2005; LANG et al., 2009).

A fragilidade pode ser vista como uma manifestação da degradação de múltiplos sistemas fisiológicos que são responsáveis pela adaptação saudável aos estresses do dia-a-dia (LIPSITZ, 2004). Durante sua progressão, as reservas fisiológicas diminuem, enquanto o aumento de recursos fisiológicos se torna necessário para reparo e manutenção do funcionamento do organismo, inevitavelmente reduzindo as reservas disponíveis remanescentes (LANG et al., 2009).

Assim, sugere-se que apesar de o processo da fragilidade ser clinicamente silencioso (LANG et al., 2009), quando as reservas fisiológicas atingem um nível crítico, o organismo se tornaria mais vulnerável aos mecanismos estressores e o risco de desfechos negativos como quedas, hospitalização, incapacidade, declínio funcional e morte aumentaria substancialmente (FRIED et al., 2001; GILL et al., 2006; VERMEIREN et al., 2016).

Frente à sua alta prevalência e aos desfechos adversos, ao longo desta última década a fragilidade emergiu como um dos “gigantes da geriatria” (MORLEY et al., 2016). Neste sentido, ampliou-se a necessidade de delinear/caracterizar esta população bem como o melhor entendimento acerca dos mecanismos subjacentes. O ciclo da fragilidade foi proposto considerando que haveria um tripé base constituído por desregulações neuroendócrina, imunológica e muscular (sarcopenia) que desencadearia uma cascata de alterações nos demais sistemas (FRIED et al., 2001). Assim, a partir disto, diversos estudos foram desenvolvidos na tentativa de mapear possíveis marcadores para a Fragilidade. Investigações em múltiplas áreas foram realizadas desde níveis celulares e sistêmicos (FOUGÈRE et al., 2015; PARVANEH et al., 2016; CHANG et al., 2017; WILSON et al., 2017) até refletir a níveis clinicamente identificáveis (SCHOON et al., 2014; SAMPAIO et al., 2015; FREIRE JUNIOR et al., 2016).

Desta forma, supriu-se parcialmente a expectativa de plena compreensão da Fragilidade. No entanto, algumas barreiras ainda persistem sobre esta síndrome como a falta de consenso do método de rastreio mais efetivo (DENT; KOWAL; HOOGENDIJK 2016; BRUYÈRE et al., 2017), bem como a ausência de marcadores biológicos específicos, assim como ocorre para o diagnóstico de algumas patologias (GAVRILA; CIOFU; STOICA, 2016; PALOMBO; KOZAKOVA, 2016). Adicionalmente, com a constatação de desfechos adversos em curto intervalo de tempo e a transição espontânea entre os estágios de Fragilidade (FRIED et al., 2001; GILL et al., 2006), reconheceu-se como indispensável o desenvolvimento de intervenções para o manejo e possível reversão da fragilidade.

Assim, diversas propostas de intervenções foram testadas, dentre elas a suplementação nutricional (BADRASAWI et al., 2016), uso de fármacos (CESARI et al., 2015) e o exercício físico (TARAZONA-SANTABALBINA et al., 2016). Este último foi apontado como a peça chave para o manejo desta síndrome (CHAN et al., 2012; DENT et al., 2017). Neste sentido, diferentes tipos de protocolos de exercício foram desenvolvidos, sendo o multicomponente identificado e recomendado como o mais adequado para esta população (DEDEYNE et al., 2017; JADCZAK et al., 2018). Dentre os principais benefícios relatados destacam-se a melhora nas funções físicas (SUGIMOTO et al., 2014), capacidade funcional (DEDEYNE et al., 2017) e status de fragilidade (BRAY et al., 2016; TARAZONA-SANTABALBINA et al., 2016).

Mediante a multidimensionalidade da Fragilidade (FRIED et al., 2009), a falta de total compreensão dos mecanismos que permeiam seu desenvolvimento, bem como das particularidades relativas ao usufruto das intervenções, sustenta-se ainda o aspecto desafiador acerca do tema. Desta forma, fundamentações têm sido propostas para melhor delinear a Fragilidade e, assim, fornecer subsídio para o estabelecimento de estratégias de manejo.

Uma das concepções teóricas da fragilidade fundamenta-se no conceito de complexidade fisiológica (LIPSITZ, 2002). O pressuposto baseia-se na noção de que as funções fisiológicas normais requerem uma complexa rede de integração entre os sistemas de controle, circuitos e mecanismos regulatórios que permitiriam um organismo apto a desempenhar suas atividades necessárias para sobrevivência (LIPSITZ, 2002). Os sistemas de controle existem em múltiplos níveis de organização (molecular, celular, orgânico e sistêmico) e suas interações garantem que haja constante troca de informação mesmo em condições de repouso. Estas interações promovem um organismo altamente adaptativo e resiliente, preparado para prontamente responder às perturbações internas e externas (LIPSITZ, 2002).

Como consequência do processo do envelhecimento, sugere-se que haja uma perda progressiva destas interações entre os sistemas fisiológicos que comprometeria as propriedades adaptativas frente aos mecanismos estressores e que caracterizaria uma reduzida complexidade (LIPSITZ; GOLDBERGER, 1992). A baixa complexidade está associada à redução no número e na conectividade dos inputs, simplificando a resposta de um sinal biológico como a frequência cardíaca (FC) e pressão arterial sistólica (PAS). Assim, uma vez que esta resposta é simplificada, ela torna-se mais previsível e consequentemente há redução da capacidade funcional do indivíduo (LIPSITZ, 2002). Acredita-se que ao atingir níveis mais críticos de complexidade, a capacidade funcional possa alcançar um nível mais inferior e cruzar o limiar da fragilidade, resultando em aumento da vulnerabilidade para cursar desfechos adversos (LIPSITZ, 2002).

Neste sentido, houve um crescente interesse na elaboração de novas métricas que pudessem descrever as dinâmicas dos sistemas fisiológicos. Entre as décadas de 90 e 00, as entropias aproximada (ApEn) (PINCUS, 1991) e de amostragem (SampEn) (RICHMAN; MOORMAN, 2000) foram desenvolvidas como forma de avaliar um dos aspectos da complexidade: a previsibilidade. Quanto mais regular o sinal, mais previsível e, portanto, menos complexo (LIPSITZ; GOLDBERGER, 1992). Outra forma de se avaliar a complexidade de um sistema são as medidas de acoplamento entre duas variáveis (VAILLANCOURT; NEWELL, 2002), como por exemplo, a interação entre FC e PAS, conhecida como barorreflexo. O barorreflexo é um dos principais mecanismos fisiológicos responsáveis pela manutenção da homeostase pressórica (NOLLO et al., 2001), e cuja avaliação também despontou como importante forma de análise da integridade do sistema nervoso autônomo (SNA) (DI RIENZO et al., 2009).

Assim, o uso de métricas de complexidade, como a entropia e sensibilidade barorreflexa (SBR) passou a ser considerado e visto como promissor para distinguir estado de saúde e patológico (LA ROVERE et al., 1998; DE FERRARI et al., 2007; HUIKURI ET AL., 2009). Um dos sistemas amplamente estudado do ponto de vista de complexidade fisiológica é o cardiovascular (LIPSITZ, 2002; PORTA et al., 2007). Além de refletir as dinâmicas de interações do SNA que é responsável pelo controle cardiovascular (MALLIANI et al., 1991), seu valor prognóstico foi identificado na predição de eventos adversos, como acidente vascular encefálico isquêmico (WATANABE et al., 2015) e infarto do miocárdio (HUIKURI et al., 2009).

Frente a isso, nos últimos anos uma maior atenção tem sido dada à fragilidade no contexto cardiovascular, visto que uma alta prevalência de sinais subclínicos de doenças cardiovasculares (DCV) foi identificada já em fases intermediárias da fragilidade (SERGI et al., 2015). Estudos recentes indicaram que ambas as condições partilham de mecanismos fisiopatológicos semelhantes e poderiam desencadear uma à outra (AFILALO et al., 2009; FLINT, 2015; FORMAN; ALEXANDER, 2016; JOYCE, 2018).

Adicionalmente, foi demonstrado um comprometimento do SNA no controle cardiovascular, refletido por alterações na variabilidade da frequência cardíaca tanto em idosos frágeis (CHAVES et al., 2008; VARADHAN et al., 2009, KATAYAMA et al., 2015), como em indivíduos com DCV (MERZ; ELBOUDWAREJ; MEHTA, 2015). Assim, a utilização de métricas baseadas na ótica da complexidade tem sido estimulada para contribuir ainda mais na compreensão da fisiopatologia da Fragilidade (WALSTON et al., 2006; LIPSITZ, 2008). Neste sentido, o uso combinado de medidas tradicionais que avaliem a integridade do SNA, como análise espectral da FC, aliada às medidas de complexidade, como o barorreflexo e a entropia poderia ser promissor.

No entanto, pouco se sabe até o momento a respeito da reversibilidade tanto do controle autonômico cardiovascular, como da complexidade fisiológica. Algumas intervenções, como o treinamento resistido foram propostas e demonstraram-se efetivas na melhora da complexidade da FC em indivíduos jovens (HEFFERNAN et al., 2007) e idosos hipertensos (MILLAR et al., 2013), enquanto na SBR divergiram (COLLIER et al., 2009; MADDEN et al., 2010). Em relação às medidas tradicionais espectrais da FC também há divergências nos achados. Em indivíduos de meia-idade, o treinamento aeróbico foi efetivo na melhora do controle cardíaco enquanto as modalidades de treinamento combinado (aeróbico e resistido) ou resistido não foram capazes de promover melhora em nenhuma das variáveis relativas à variabilidade da frequência cardíaca (KARAVIRTA et al. 2013). Até o presente momento, desconhece-se a efetividade das intervenções, tanto nas medidas tradicionais de controle cardiovascular quanto de medidas de complexidade em idosos pré-frágeis.

Dado o caráter multissistêmico da condição de Fragilidade (FRIED et al., 2009), bem como o papel crucial do SNA sobre o controle dos diversos sistemas fisiológicos (WALSTON et al., 2006), a abordagem de treinamento baseada em exercício multicomponente poderia ser promissora considerando seu perfil global e abrangente, possibilitando a restauração das dinâmicas responsáveis pelo controle cardiovascular e consequentemente refletiria nas medidas lineares tradicionais (análise espectral), bem como na complexidade (SampEn e SBR).

Baseado neste contexto, esta tese foi planejada e desenvolvida em dois estudos. O **Estudo I** intitulado *"Multicomponent exercise training does not improve cardiovascular control in prefrail older adults: a blinded randomized clinical study"* teve como objetivo investigar se uma intervenção multicomponente de 16 semanas promoveria melhora no controle cardiovascular de idosos pré-frágeis, avaliados por medidas tradicionais como a análise espectral da FC e da PAS.

Adicionalmente, investigou-se se o treinamento multicomponente poderia repercutir em mudança na complexidade das dinâmicas cardiovasculares (SampEn e BRS). Assim, para responder esta lacuna, o **Estudo II** foi idealizado e elaborado, intitulado *"Multicomponent exercise training in cardiovascular complexity in prefrail older adults: a blinded randomized clinical study"*. Este estudo teve por objetivo avaliar se o treinamento multicomponente seria efetivo na restauração da complexidade cardiovascular (SampEn e SBR).

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2. ESTUDO I

(Versão em inglês apresentada nas normas da revista)

MULTICOMPONENT EXERCISE TRAINING DOES NOT IMPROVE CARDIOVASCULAR CONTROL IN PREFRAIL OLDER ADULTS: A BLINDED RANDOMIZED CLINICAL STUDY

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ABSTRACT

This study aimed to investigate the effects of multicomponent training on cardiovascular control and performance on the 6-minute walk test (6MWT) of prefrail older adults. Twenty-one prefrail community-dwelling older adults were randomized and divided into multicomponent training intervention group (MulTI) and control group (CG). MulTI performed multicomponent training over 16 weeks and CG was oriented to follow their own daily activities. Walk distance in 6MWT was collected. The RR interval (RRi) and blood pressure (BP) series were recorded for 15 min in supine and 15 min in orthostatic positions. Spectral analysis of RRi and BP were performed. A linear mixed model was applied for group, position, and their interaction effects. The significance level established was 5%. Significant interactions were not observed between groups or assessments in terms of cardiovascular parameters. There was no effect of the intervention on functional performance of the 6MWT. Multicomponent exercise intervention was not capable to improve cardiovascular control even in supine rest as well in active postural maneuver in prefrail older adults.

KEYWORDS

Aging; autonomic nervous system; frailty; physical exercise.

2.1. INTRODUCTION

Frailty is a distinct geriatric syndrome, described as a clinical state of vulnerability to stress, as consequence of decline of resilience and physiologic reserve related to aging (Fried et al., 2001; Lipsitz, 2004). This clinical condition is a result of cumulative decline in many physiological systems during a life-course (Clegg et al., 2013) and is associated to increased risk of adverse outcomes such as mortality, falls, institutionalization, hospitalization, loss of independence and progressive decline in homeostasis (Fried et al., 2001; Lipsitz, 2004).

The homeostasis maintenance depends on a healthy autonomic nervous system (ANS) which is featured by effective capacity on adaptability and plasticity to daily stressful conditions (Manor and Lipsitz, 2013). One of the main systems strongly influenced by ANS is the cardiovascular (Malliani et al., 1991). Thus, a dysregulation in ANS could imply greater risk of arrhythmia, myocardial infarction and disease development (La Rovere et al., 1998; Suchy-Dicey at al., 2013). Previous studies demonstrated impairment in ANS among prefrail and frail individuals (Chaves et al., 2008; Varadhan et al., 2009; Katayama et al., 2015; Parvaneh et al., 2015).

Recently, it has been discussed an association into cardiovascular outcomes and frailty. It seems these both conditions share common physiological pathways and each one may lead to the other in a vicious cycle leading to poor outcomes (Afilalo et al., 2009; Flint, 2015). Therefore, the early detection of frailty becomes of major relevance once the intermediate state (prefrailty) already demonstrated an increased risk for incident cardiovascular disease (CVD) (Sergi et al., 2015). This suggests that targeting pre-frailty could have significant implications concerning prevent CVD (Sergi et al., 2015), as well as progression of higher levels of frailty.

Considering the dynamic and gradual progression of frailty into different levels (Gill et al., 2006), the earliest management is indispensable. In this sense, physical exercise has been demonstrated as crucial and the best approach especially in prefrail (Chan et al., 2012; Dent et al., 2017). Despite the several kind of interventions proposed, the multicomponent has been described as the most beneficial in terms of physical domain, functional performance or frailty status transitions (Cadore et al., 2014; Sugimoto et al., 2014; Bray et al., 2016; Dedeyne et al., 2017; Jadcazk et al., 2018).

Nonetheless, it remains unknown if a multicomponent intervention could induce improvement in ANS on cardiovascular control. Thus, the primary aim of this study was to verify if a 16-week multicomponent training would present effect in cardiovascular control in prefrail older adults. Furthermore, the secondary aim was to verify if that training could impact on functional performance of the 6-minute walk test (6MWT).

2.2. METHODS

2.2.1 Sample

This blinded randomized controlled trial was properly registered (Clinical Trial Registration ID: xxxxxxxxxxx) and approved by the Research Ethics Committee of the institution (ID: xxxxxxx). Written consent was obtained from all the volunteers. All procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration.

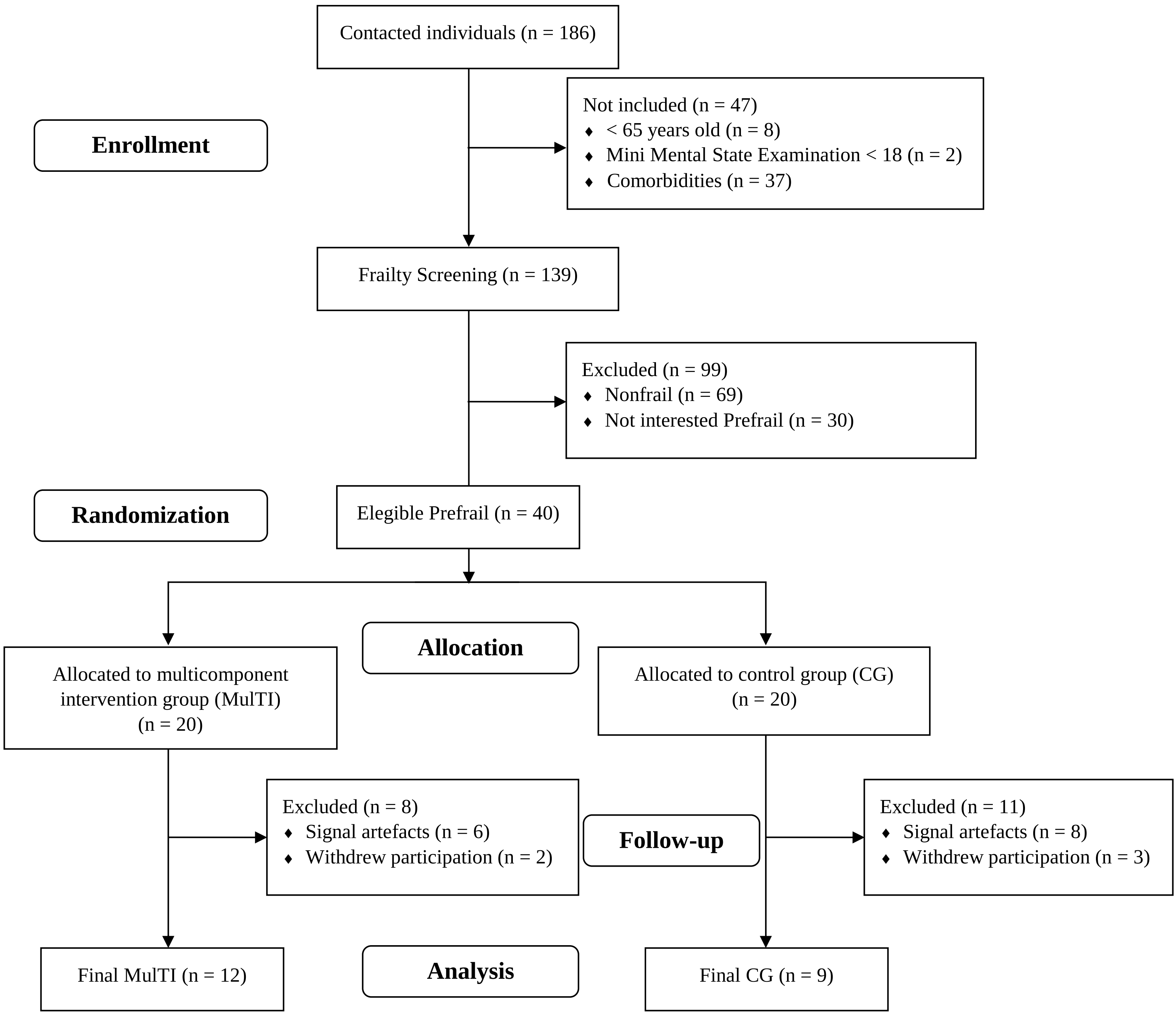
The volunteers' recruitment was carried out in 2016-2018 through posters delivered to churches, drugstores, geriatric outpatient clinics, and primary healthcare local.

The inclusion criteria were prefrail according to frailty phenotype (Fried et al., 2001) community-dwelling older adults ($\geq$ 65 years old), medical release for exercise and agree to participate in the study. The non-inclusion criteria were a) Parkinson's disease; b) stroke; c) Diabetes mellitus with peripheral neuropathy (Wayne et al., 2013) assessed by Semmes-Weinstein monofilaments 5.07 (10g) (Souza et al., 2005); d) Vestibular and visual self-reported disorders that would impair performance in assessment and/or training; e) an indication of cognitive deficit, which will be assessed by means of the Mini Mental State Examination (MMSE) with scores lower than 18 (Fried et al., 2001); f) cardiovascular alterations (atrial fibrillation, malignant ventricular arrhythmia, complex ectopic ventricular beat, sinus or supraventricular tachycardia, second and third degree atrioventricular block; g) use of a pacemaker on resting electrocardiogram (ECG); h) unstable angina; i) myocardial infarction.

Figure 1 shows a flowchart of the sample. Initially, 186 older adults were contacted. Forty-seven were not included due age, comorbidities according to criteria and MEEM score < 18. Frailty screening was applied in 139 individuals and 99 were excluded due frailty status or not interest in study. Thus, 40 were considered eligible prefrail. They were randomized into two groups that included 20 subjects in the multicomponent intervention group (MulTI), who participated in a multicomponent physical exercise protocol and 20 participants in the control group (CG), which was oriented to follow their own habitual daily activities. After data analysis and exclusion by withdrew participation (desistance) and signal artefacts, the final sample was composed by 21 subjects: MulTI (n = 12) and CG (n = 9).

Initially, a pre-interview was conducted to identify the eligible individuals considering the non-inclusion criteria. Once the individual was in accordance and fulfilled the criteria, he would be invited to participate of the study.

Figure 1 - Flowchart of the final sample



2.2.2 Anamnesis

All participants were submitted to a structured interview. Demographic data (age, ethnicity and sex), educational level, comorbidities, medicine use were collected.

2.2.3. Assessment

After the initial assessments, the participants were randomly distributed by software Random Allocation into blocks of eight subjects. According to the randomization sequence, each participant corresponded to an opaque and sealed envelope, numbered in order, containing a card indicating which group the individual would be inserted (MulTI or CG). The entire randomization process was performed by a researcher who had no link to the study (J.H.A.). The envelopes were opened after the first evaluation and the researchers were blinded about the allocation of the participants.

The assessments were performed in two distinct times: 1) pre-intervention (initial assessment) and post-intervention (immediately after the conclusion of the 16-week multicomponent intervention).

2.2.4. Six-Minute Walk Test (6MWT)

The 6MWT is used to assess the submaximal exercise capacity of individuals from the longest distance walked in six minutes (ATS, 2002). Data was collected regarding the walk distance (WD) by volunteers and scores of dyspnea and fatigue of lower limbs by the 0-10 scale of Borg (Borg, 1998), which was previously explained to the patient, being 0 no symptoms and 10 the maximum symptom perceived by the same. For the 6MWT, the recommendations for the 6MWT were followed according to the American Thoracic Society (ATS, 2002).

2.2.5. Procedures and experimental protocol for ANS assessment

Initially, the volunteers were instructed to remain in supine position for 10 minutes in order to stabilize cardiovascular variables and to conduct the calibration procedure. ECG, blood pressure (BP) and breathing recordings were collected for 15 minutes in supine position. Then, the volunteers were instructed to actively change to orthostatic position, in which they remained for 15 minutes. They were also instructed to breathe spontaneously, not to talk unnecessarily and remain awake during the test.

The experiments were conducted in a climate-controlled (22-23°C) room with relative air humidity of 40-60% always in the morning in order to minimize circadian cycle effects. Familiarization procedures were performed so the volunteers would feel comfortable with the experimental protocols, technical people, equipment, and materials. Each volunteer was instructed prior to the experiments not to ingest caffeine or alcohol, not to perform moderate or heavy exercise on the day before participation and have a regular meal.

2.2.6. Signal acquisition

The ECG signal was collected by a bioamplifier (BioAmp Power Lab - Ad Instruments, Australia) with electrodes placed on the MC5 lead, and respiratory movements were captured by a respiratory belt (Marazza, Monza, Italy). The arterial BP waves were obtained by a plethysmography arterial pressure device (Finometer PRO, Finapress Medical Systems, The Netherlands), with a cuff placed on the distal extremity of the right middle finger. This hand was kept close to the volunteer’s heart with the help of a sling, which fixed the volunteer’s arm to his chest throughout the experiment. The signal acquisition frequency was sampled at 1000 Hz.

The extraction of beat-to-beat variability series was carried out according to previous descriptions (Faes et al., 2013). After extraction of the series, 256-points sequences with the greatest stability were chosen for both positons (Task Force, 1996).

2.2.7. Data analysis

The RRi and BP’s mean and variance were calculated, as well as a spectral analysis was conducted through the auto regressive method (Pagani et al. 1986; Malliani and Montano, 2002). The low frequency band (LF) oscillates between 0.04-0.15 Hz and is related to the combined modulation of sympathetic and parasympathetic, with sympathetic predominance. The high frequency band (HF) oscillates between 0.15 - 0.40 Hz and relates to parasympathetic and respiratory modulation (Task Force, 1996). In this study, for RRi variability was used HF and LF in normalized units (HFnu and LFnu, respectively) and the LF/HF ratio which corresponds to sympathetic and parasympathetic balance (Task Force, 1996). Regarding BP variability was used LFabs (Malliani and Montano, 2002).

2.2.8. Intervention Protocol

The multicomponent exercise intervention was designed considering the recommendations proposed by American College of Sports Medicine (ACSM, 2009). The protocol consisted on aerobic, muscle strength, flexibility, and balance exercises. It was applied during 16 weeks, for three non-consecutive days, with 60-minute sessions. The sessions were composed by: a) 10 minutes of warm-up (light walk); b) 20 minutes of aerobic exercises; c) 10 minutes of balance exercise; d) 15 minutes of resistance exercises; e) 5 minutes of warm-down. Details concerning exercise type, intensity and progression are described in table 1.

Table 1 - Structure of the protocol of the Multicomponent Training Intervention group

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 started at 45% HRR in the first two weeks and increased by 5% every two weeks until reaching 80% HRR (Toraman, & Ayceman, 2005). During the training sessions, the THR was 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 protection strategies (ankle, hip, and step).	If necessary, a physiotherapist manually induced a slight unbalance.	The progression of these exercises was 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) (ACSM, 2009), 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; strengthening for the upper limbs; 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 followed the same criterion of progression mentioned in the familiarization (through the Borg CR-10 Scale).
Warm-down (5 minutes)	Breathing exercises and overall stretching.	30-60s of static stretching (ACSM, 2009)	Until reaching resting HR and BP

Before the beginning of the intervention, all volunteers of the MulTI were invited to participate of three sessions in non-consecutive days for familiarization process and determination of resistance training load. The participants should perform one set of 8 repetitions without additional weight and report the level of effort according to the Borg CR-10 scale (Borg, 1998). If the score was into 5 to 8, the repetitions as well as the load would be maintained for the first two weeks of the resistance training. If below 5, the number of repetitions would be progressively increased until 12. If the volunteer reported a score below 5 even after the 12 repetitions performed, a 0.5-kg load would be added to the involved limb or segment (Giné-Garriga et al., 2014). This procedure was performed individually for each exercise: (i) sit to stand from the chair; (ii) strengthening exercises for the upper limbs; (iii) calf exercises; (iv) lunges; (v) step up and step down. Halters and a special waistcoat (vest) with large pockets (where ankle weights could be inserted) were used to facilitate the exercise execution and load increase.

For aerobic component, the training started at 45% of heart rate reserve (HRR) in the first two weeks and increased by 5% every two weeks until reaching 80% HRR (Toraman and Ayceman, 2005). Participants used a cardiac frequency monitor (Polar® S810i) during walking on the ground or on the treadmill.

The progression for balance component was performed concerning 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) (ACSM, 2009), changes in the direction and speed, and overload of muscular groups involved in the posture (walking on tiptoe, heel).

And related to flexibility, exercises were applied for global muscles groups until reach the resting HR and BP associated to breathing.

2.2.9. Statistical analysis

Sample size was based on previous study (Katayama, Dias, Silva, Virtuoso-Junior, & Marocolo, 2015) which presented cardiovascular parameters as main outcome in prefrail and frail population.

The Shapiro-Wilk test was used to verify the normality of data distribution. An Independent T-test was used to compare age, anthropometric characteristics (weight, stature, BMI) and number of comorbidities at baseline. A chi-square test was applied to compare sex.

A linear mixed model test was used in order to assess the effect of the training at the pre and post-intervention, between MulTI and CG on cardiovascular variables in supine rest position, and on 6MWT walk distance. Besides, the same test was used to assess the effect on postural maneuver separately for each group, considering assessments (pre x post) and positions (supine x orthostatic).

The significance level established was 5%. Statistical analysis was performed using the software IBM SPSS Statistics, version 20.0 (Armonk, NY, USA, 2011).

2.3. RESULTS

The volunteers' age, anthropometric, and clinical characteristics are presented in table 2. There was no difference in sex, age, body mass, stature, number of comorbidities between the groups. There was significant difference only for BMI ($p = .032$) and for walk distance in 6MWT ($p = .011$) between the groups.

Table 2 - Age, anthropometric and clinical characteristics

	MulTI (*N* = 12)	CG (*N* = 9)	P value
Female gender, *N* (%)	10 (83.3)	5 (55.6)	.163
Age (y)	77.00 ± 6.80	73.78 ± 6.28	.281
Body mass (kg)	76.26 ± 12.72	68.54 ± 8.69	.135
Stature (cm)	154.83 ± 6.48	159.56 ± 5.90	.102
BMI (kg/m^2)	31.95 ± 5.47	27.02 ± 3.74	**.032**
Comorbidities	2.33 ± 1.30	2.44 ± 1.81	.872
6MWT walk distance (m)	326.42 ± 64.42	401.00 ± 53.18	**.011**

Notes: Values are expressed as mean ± standard deviation or total of individuals (percentile). y = years; BMI = body mass index; CG = control group; MulTI = multicomponent training intervention group; 6MWT = 6-minute walk test.

Still related to the walk distance in 6MWT, CG performed 401.00 m in pre and 414.00 m in post assessment, while MulTI performed 326.42 m in pre and 323.50 in post assessment. CG presented significant higher 6MWT walk distance in comparison to MulTI (p = .019). There was no difference between assessments (p = .741) or interaction (p = .375).

Table 3 presents time domain (mean and variance of RRi and BP) and frequency domain parameters (BP LFabs, RRi LFnu, RRi HFnu, LF/HF) in rest supine position. In terms of BP and RRi, no difference was observed into groups or assessments.

Table 3 - Time domain and frequency domain of RRi and BP in supine position

	MulTI		CG		P-value		
	Pre	Post	Pre	Post	Groups	Assessments	Interaction
RRi							
Mean (ms)	953.82 ± 98.26	910.34 ± 134.15	889.11 ± 155.08	915.87 ± 147.91	.644	.308	.158
Variance (ms^2)	331.95 ± 319.74	340.68 ± 443.75	456.01 ± 352.85	585.12 ± 554.14	.079	.112	.543
LFnu	55.34 ± 25.58	64.85 ± 17.50	55.49 ± 25.41	71.84 ± 15.03	.432	.179	.725
HFnu	42.80 ± 24.77	32.38 ± 16.77	40.19 ± 22.41	27.06 ± 14.51	.777	.269	.983
LF/HF	3.05 ± 3.79	3.37 ± 3.57	3.84 ± 4.18	6.82 ± 10.91	.771	.904	.478
BP							
Mean (mmHg)	126.68 ± 19.39	119.21 ± 20.06	134.06 ± 22.33	127.87 ± 16.29	.347	.403	.969
Variance ($mmHg^2$)	35.52 ± 30.25	19.73 ± 14.70	37.05 ± 20.99	36.01 ± 28.59	.100	.112	.191
LFabs	3.58 ± 2.09	2.21 ± 3.49	7.65 ± 7.49	5.98 ± 7.23	.087	.722	.364

Notes: Values are expressed as mean ± standard deviation. BP = blood pressure; CG = control group; HFnu = high freqyency in normalized units; LF/HF = low frequency-high frequency ratio; LFabs = low frequency in absolute units; LFnu = low frequency in normalized units; MulTI = multicomponent training intervention group; RRi = RR interval.

The postural maneuver behavior of each group between assessments was reported in Tables 4 and 5. Both present the same data of the cardiovascular parameters of previous table. The CG did not present significant differences for position, assessment or interaction in none of BP or RRi parameters (table 4). On the other hand, there was a position effect for BP LFabs (orthostatic > supine; $p = .022$) in MulTI. No additional difference was identified for another variable (table 5).

Table 4 - Time domain and frequency domain of RRi and BP in Control Group

	PRE		POST		P-value		
	Supine	Orthostatic	Supine	Orthostatic	Position	Assessments	Interaction
RRi							
Mean (ms)	889.11 ± 155.08	777.92 ± 222.43	915.87 ± 147.91	838.90 ± 148.98	.187	.187	.625
Variance (ms^2)	456.01 ± 352.85	438.30 ± 577.31	585.12 ± 554.14	312.54 ± 337.41	.936	.444	.228
LFnu	55.49 ± 25.41	64.10 ± 23.18	71.84 ± 15.03	81.35 ± 13.07	.389	.053	.921
HFnu	40.19 ± 22.41	30.40 ± 18.78	27.06 ± 14.51	17.64 ± 25.04	.266	.074	.826
LF/HF	3.84 ± 4.18	2.63 ± 1.95	6.82 ± 10.91	7.50 ± 6.41	.722	.210	.725
BP							
Mean (mmHg)	134.06 ± 22.33	136.82 ± 23.96	127.87 ± 16.29	144.47 ± 24.90	.796	.421	.353
Variance ($mmHg^2$)	37.05 ± 20.99	50.45 ± 43.35	36.01 ± 28.59	42.92 ± 18.96	.410	.743	.958
LFabs	7.65 ± 7.49	9.42 ± 11.53	5.98 ± 7.23	12.03 ± 16.11	.751	.646	.582

Notes: Values are expressed as mean ± standard deviation. BP = blood pressure; HFabs = high frequency in absolute units; LF/HF = low frequency-high frequency ratio; LFabs = low frequency in absolute units; LFnu = low frequency in normalized units; RRi = RR interval.

Table 5 - Time domain and frequency domain of RRi and BP in Multicomponent Training Intervention group

	PRE		POST		P-value		
	Supine	Orthostatic	Supine	Orthostatic	Position	Assessments	Interaction
RRi							
Mean (ms)	953.82 ± 98.26	901.86 ± 126.25	910.34 ± 134.15	846.71 ± 145.15	.332	.296	.973
Variance (ms^2)	331.95 ± 319.74	282.66 ± 149.52	340.68 ± 443.75	182.66 ± 90.26	.678	.446	.548
LFnu	55.34 ± 25.58	55.07 ± 23.21	64.85 ± 17.50	57.61 ± 24.30	.977	.802	.579
HFnu	42.80 ± 24.77	40.82 ± 21.60	32.38 ± 16.77	35.44 ± 20.57	.820	.557	.672
LF/HF	3.05 ± 3.79	2.58 ± 3.09	3.37 ± 3.57	6.07 ± 10.37	.841	.158	.350
BP							
Mean (mmHg)	126.68 ± 19.39	132.11 ± 20.08	119.21 ± 20.06	135.76 ± 20.08	.507	.686	.369
Variance ($mmHg^2$)	35.52 ± 30.25	45.92 ± 33.37	19.73 ± 14.70	31.26 ± 18.46	.329	.143	.962
LFabs	3.58 ± 2.09	10.09 ± 10.85	2.21 ± 3.49	6.42 ± 6.85	**.022**	.183	.527

Notes: Values are expressed as mean ± standard deviation. BP = blood pressure; HFabs = high frequency in absolute units; LF/HF = low frequency-high frequency ratio; LFabs = low frequency in absolute units; LFnu = low frequency in normalized units; RRi = RR interval. [*]P < 0.05 supine in comparison to orthostatic position.

2.4. DISCUSSION

Considering the overall systemic aging process, older adults tend to develop a chronic activation of sympathetic branch (Seals and Dinenno, 2004) which has deleterious effects on cardiovascular system such as reduced leg blood flow, increased arterial blood pressure, impaired baroreflex and hypertrophy of main arteries (Garatachea et. al, 2015). Additionally, an inability to produce β-adrenergic-mediated peripheral vasodilation in response to epinephrine release could limit the physiological adjustments to physical stress (Seals and Dinenno, 2004), as well postural maneuver. Frail individuals present deterioration of ANS on cardiovascular control observed by a higher sympathetic modulation even in supine rest condition (Katayama et al., 2015; Parvaneh et al., 2016). It's possible that in prefrail these physiological changes could already be present even in minor proportion, which would reflect in cardiac control deficit response. As demonstrated by both groups, none of them presented the expected heart rate behavior after the postural maneuver.

Active postural maneuver is one the most common and simple test for ANS assessment (Perseguini et al., 2011; Moura-Tonello et al., 2014). In Frailty research it has been suggested the usage of provocative or stressful tests to evaluate the homeostasis capacity (Lipsitz, 2002; Walston et al., 2006). To guarantee homeostasis it's crucial an integration among the biological systems. In healthy organisms this integration occurs naturally and the individuals keep a physiologic reserve that allows most of them to compensate effectively for age- and disease-related changes (Lipsitz, 2002). Aging process is accompanied by a reduction in reserve capacities of all systems but the organism is capable to readjust a physiological response. In Frailty a functional reserve threshold is reached and this ability may be damaged. Thus, impairment in physiological response is expected (Lipsitz, 2002) as well it was observed in ANS response to active postural maneuver by prefrail individuals of present study.

Considering the cardiovascular system, the functional reserve is a major determinant of the individual's capacity to exercise or remain active and provides the ability to cope with daily stresses (Lipsitz, 2002; Goldspink, 2005). At critical thresholds routine daily tasks gradually become difficult and individuals may be susceptible to develop arrhythmia and postural hypotension (Lipsitz, 2002) which is most prevalent in prefrail and frail individuals (Romero-Ortuno et al., 2011; O'Connell et al., 2015). Despite the attenuated/less responsiveness of HR and BP control to postural maneuver presented in both CG and MulTI, all these individuals may still preserve a minimum of functional reserve which allowed the active postural change without intercurrences. The MulTI already responded with increase of sympathetic modulation in BP before and maintained even after the intervention, which suggests there was no influence of the multicomponent training in BP control.

It's already well established the beneficial effects of physical exercise on structural and functional domains of older adults (Heckman and McKelvie, 2008; ACSM, 2009; Viña et al., 2016; Rebelo-Marques et al., 2018). Into the wide types of exercise training mentioned in literature, the most common cited with repercussions in cardiovascular control is the aerobic-based (Seals et al., 2009; Hellsten and Nyberg, 2015). The available evidence indicates that aerobic training tends to generate beneficial effect on arterial stiffness (Li et al., 2015), cardiac functional reserve and overall aerobic capacity (Goldspink, 2005). The regular practice of aerobic exercise could preserve or restore endothelium dilatation by increasing nitric oxide bioavailability, besides may act to preserve vascular function with advancing age by protecting arteries from the adverse effects of conventional risk factors for CVD (Seals et al., 2009).

Meanwhile, there are some divergent findings regarding the type of exercise intervention and cardiovascular outcomes according to the target population. In pre to essential hypertensive middle-age individuals no difference it was observed for RRi LF or HF after 4-week resistance training (Collier et al., 2009), while RRi HF increases after 4-week aerobic training. Additionally, in middle-age and older men, a 3-month aerobic intervention it was not capable to change any parameters of RRi (Monahan et al., 2000). On the other hand, the combined strength plus endurance training or the strength training alone did not produce significant changes in spectral parameters of HR in middle-age and older adults (Karavirta et al., 2013).

Thus, although the distinct cardiovascular benefits of exercise training in older adults as above mentioned, few researches has focused on Frailty. Given the multidimensionality of Frailty Syndrome, the resistance (Zech et al., 2012) and the multicomponent training (Dedeyne et al., 2017; Jadcazk et al., 2018) has been indicated as the most effective interventions. Therefore, the protocol design of the present study was carefully elaborated, targeting prefrail older adults considered as the potential population to extract the major benefits of an intervention (Theou et al., 2011). Nevertheless the cardiovascular effects on this population remains unknown in the literature, once the main outcomes generally described are about physical domains, functional performance or frailty status (Zech et al., 2012; Sugimoto et al. 2014; Tarazona-Santabalbina et al., 2016).

To date, it is unknown if prefrail individuals present specificities related to physiological adaptations to exercise different from healthy older adults. In a 6-month of resistance-based training, healthy 60-83 years old increased peak oxygen uptake (VO_2 peak) by 23.5% in low-intensity exercise group and counterpoint to 20.1% in high-intensity exercise group (Vincent et al., 2002). A 3-month multicomponent training was not capable to improve aerobic capacity among frail older adults (Rydwik et al., 2010). On the other hand, in mild to moderate frail octogenarians, a combined training of endurance and strength promoted an increase of 14% in VO_2 peak, which was considered by the authors as small adaptive response compared to younger individuals (Binder et al., 2002; Ehsani et al., 2003). Thus, prefrailty condition per se might influence the potential effectiveness of the different training programs (Rydwik et al., 2010; Garatachea et al., 2015), as well as observed in the present study. There was not an improvement in cardiovascular control in supine rest position as well in active postural maneuver even after 16-week of multicomponent training.

On the other hand, the multicomponent training was not harmful for autonomic control of prefrail individuals. The ACSM (2009) statement suggests at least 150 minutes/week of moderate-intensity aerobic exercises for older adults (ACSM, 2009). Considering the aerobic component performed weekly by the MulTI (approximately 60 minutes) and the progression according the individual training HR, it may have not been enough to produce benefits in ANS. In consonance this is also notable in 6MWT performance, once no improvement was identified for MulTI. Nevertheless, it might be highlighted the protocol design proposed the usage of accessible low cost material, which allows the easy reproducibility in environment like primary health care. Besides, the functional feature of the intervention seems to be meaningful for older adults, once the benefits are more clearly evident in their activities daily life and this motivation may contributes to adoption of an active lifestyle.

Thus, it should be encouraged the development of interventions considering the specificities related to prefrailty. Due to global character, it might be recommended to target in generalized approach in a first moment, whereas multiple deficits could be present. Thereby, once the individual possibly restores a minimum physiological reserve and achieves a suitable condition, he could be addressed to a specific approach (e.g, aerobic or balance domain) to improve until a higher level desirable for healthy older adults.

2.5. LIMITATIONS

The cardiopulmonary exercise testing, which is considered as gold standard tool for determination of maximal oxygen uptake (VO_2 max), was not performed to assess aerobic capacity.

2.6. CONCLUSION

A 16-week multicomponent exercise intervention was not capable to improve cardiovascular control in prefrail older adults. No difference was observed neither BP or RRi parameters as well as 6MWT performance. Considering the postural maneuver, both MulTI and CG presented a deficit in HR response. This indicates a possible impairment already presented in earlier stages of Frailty. In this sense, future studies should be conducted aiming to investigate cardiovascular effects of different type of intervention, as well the duration, load training and the residual effects in prefrail individuals.

2.7. CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest.

2.8. FUNDING

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2.10. HIGHLIGHTS

- Prefrailty is related to a deficit in autonomic nervous system adjustment.
- Prefrail presented an impaired cardiovascular response to postural maneuver.
- Multicomponent intervention was not capable to improve cardiovascular control.
- There was no improvement in six-minute walk test performance after intervention.

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3. ESTUDO II

(Versão em inglês apresentada nas normas da revista)

MULTICOMPONENT EXERCISE TRAINING IN CARDIOVASCULAR COMPLEXITY IN PREFRAIL OLDER ADULTS: A BLINDED RANDOMIZED CLINICAL STUDY

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ABSTRACT

Objective: To investigate the effects of multicomponent training on baroreflex sensitivity (BRS) and heart rate (HR) complexity of prefrail older adults. Methods: Twenty-one prefrail community-dwelling older adults were randomized and divided into multicomponent training intervention group (MulTI) and control group (CG). MulTI performed multicomponent training over 16 weeks and CG was oriented to follow their own daily activities. Walk distance in the 6-minute walk test (6MWT) and speed gait were collected. The RR interval (RRi) and blood pressure (BP) series were recorded for 15 min in supine and 15 min in orthostatic positions and calculation of BRS (phase, coherence and gain) and HR complexity (sample entropy) were performed. A linear mixed model was applied for group, assessments and their interaction effects in supine position. The same test was used to assess the active postural maneuver and it was applied separately to each group considering assessments (baseline and post intervention) and positions (supine and orthostatic). The significance level established was 5%. Results: Cardiovascular control is impaired in prefrail older adults in supine position. Significant interactions were not observed between groups or assessments in terms of cardiovascular parameters. Conclusion: Multicomponent exercise intervention was not capable to improve HR complexity or BRS even in supine rest as well in active postural maneuver in prefrail older adults. Nonetheless, for those who did not train the complexity reduced suggesting to not training could impair even more these interactions of cardiac control.

Keywords: Aging, baroreflex, complexity, frailty, physical exercise.

3.1 Introduction

There is accumulating evidence that Frailty may become one of the world's most serious health issues (Dent, Kowal, & Hoogendijk, 2016). A quarter to half of people older than 85 years are estimated to be frail (Song, Mitnitski, & Rockwood, 2010). Considering the expansive increase in older adults in overall world, Frailty prevalence tends to rise considerably (Morley et al., 2013) and consequently a burden on health and aged care systems are also expected (Clegg, Young, Iliff, Rikkert, & Rockwood, 2013; Dent, Kowal, & Hoogendijk, 2016).

In this sense, Frailty appears as one of the most problematic condition, described as a clinical state of vulnerability to stress, as consequence of decline of resilience and physiologic reserve related to aging (Fried et al., 2001; Lipsitz, 2004; Clegg, Young, Iliff, Rikkert, & Rockwood, 2013). Frailty has been considered as a consequence of cumulative decline in many physiological systems during a lifetime (Clegg, Young, Iliff, Rikkert, & Rockwood, 2013) resulting in increased risk of adverse outcomes such as mortality, falls, institutionalization, hospitalization, loss of independence and progressive decline in homeostasis (Fried et al., 2001; Lipsitz, 2004).

The maintenance of homeostasis depends on a complex network of interactions between the control mechanisms. Aging process is accompanied by a reduction of these interactions into the physiological systems, which limits adequate response to stressors and characterize the organism as reduced physiological complexity (Lipsitz & Goldberger, 1992; Lipsitz, 2002). In frailty, it is suggested a loss of physiological complexity even more pronounced, which would induce a loss of functional capacity to critical levels. Thus, the individual would become less resilient and therefore more vulnerable to development of pathologies and adverse outcomes as above-mentioned (Lipsitz, 2002).

Currently, the study of complexity has been suggested in addition to traditional measurements in biological and health research (Walston et al., 2006). Once the physiological systems present a dynamic behavior, the complexity approach may offer an opportunity to characterize qualitatively these interactions (Lipsitz, 2002) as well baroreflex sensitivity (BRS) may represent interactions for blood pressure (BP) control. In this sense, one of the main physiological systems most studied is the cardiovascular (Lipsitz, 2002; Porta et al., 2010). It has already been demonstrated frail older adults presented impairment in cardiac complexity (Lipsitz, 2004; Chaves et al., 2008; Katayama, Dias, Silva, Virtuoso-Junior, & Marocolo, 2015) and in BRS (Buto et al., 2019).

Into the several interventions designed to frail and prefrail older adults, the multicomponent exercise training has been demonstrated as the most effective considering reversion of frailty status and benefits in physical domains (Dedeyne et al., 2017; Jadcazk, Makwana, Luscombe-Marsh, Visvanathan, & Schultz, 2018). Nonetheless, the underlying physiological mechanisms remained unclear. To date there are few and divergent information about reversibility of cardiovascular complexity. Resistance training was effective in heart rate (HR) complexity improvement in young individuals as well hypertensive older adults (Heffernan, Fahs, Shinsako, Jae, & Fernhall, 2007; Millar, Levy, McGowan, McCartney, & MacDonald, 2013), in counterpoint did not improve BRS in middle-aged (Collier et al., 2009).

Thus, it remained unknown if an exercise intervention could promote benefits in cardiovascular complexity in prefrail individuals. In this sense, the aim of the present study was to verify if multicomponent exercise training could restore HR complexity as well BRS in prefrail older adults.

3.2. Methods

3.2.1. Ethical Approval

This blinded randomized controlled trial was properly registered (Clinical Trial Registration ID: NCT03110419) and approved by the Research Ethics Committee of the institution (ID: 1800231/2016). Written consent was obtained from all the volunteers. All procedures were performed in accordance with the ethical standards of the 1964 Helsinki Declaration.

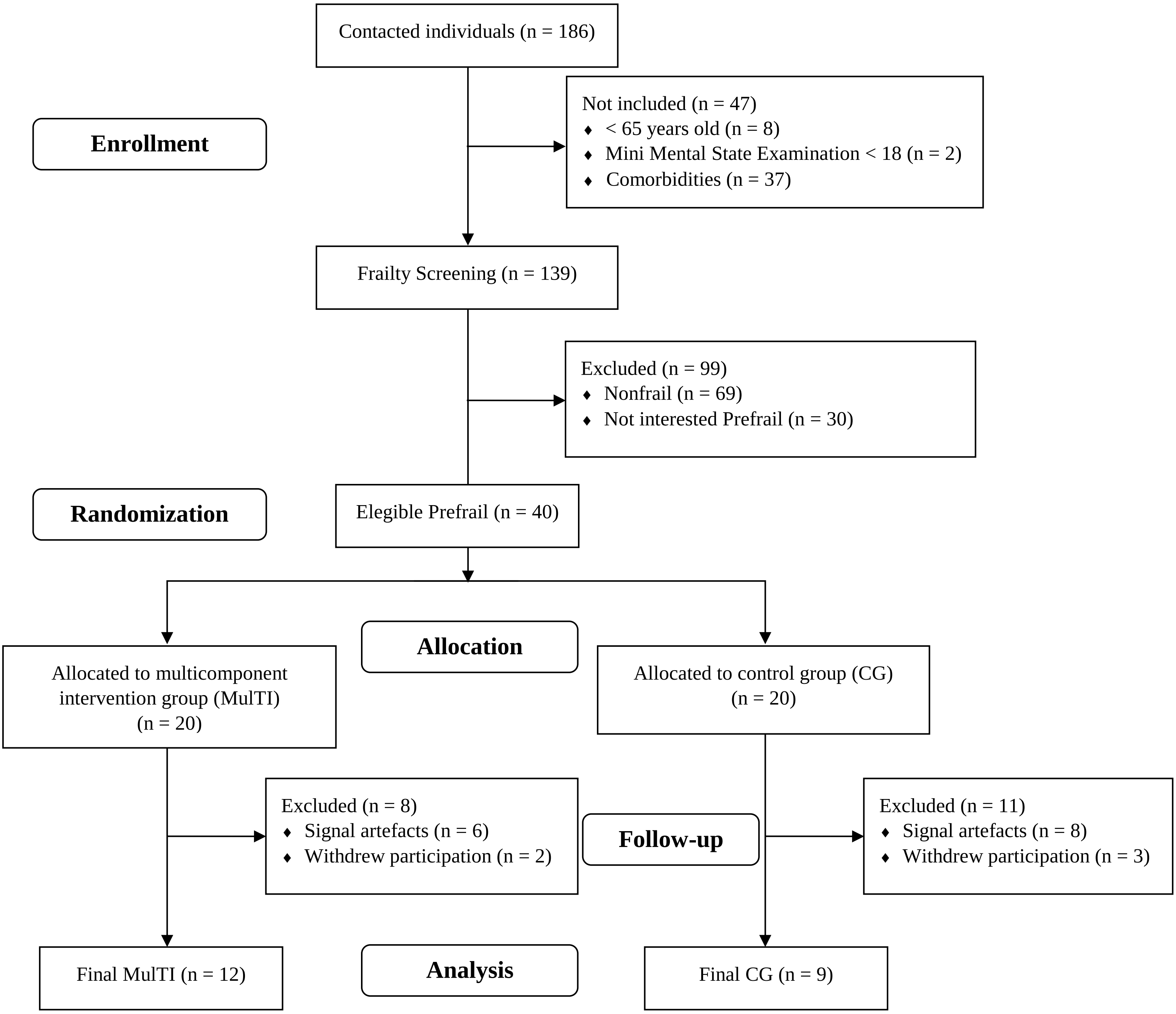
3.2.2. Sample

The inclusion criteria were prefrail according to frailty phenotype[5] community-dwelling older adults (≥ 65 years old), medical release for exercise and agree to participate in the study. The non-inclusion criteria were a) Parkinson's disease; b) stroke; c) Diabetes mellitus with peripheral neuropathy (Wayne et al., 2013) assessed by Semmes-Weinstein monofilaments 5.07 (10g) (Souza, Nery, Marciano, & Garbino, 2005); d) Vestibular and visual self-reported disorders that would impair performance in assessment and/or training; e) an indication of cognitive deficit, which will be assessed by means of the Mini Mental State Examination (MMSE) with scores lower than 18 (Fried et al., 2001); f) cardiovascular alterations (atrial fibrillation, malignant ventricular arrhythmia, complex ectopic ventricular beat, sinus or supraventricular tachycardia, second and third degree atrioventricular block; g) use of a pacemaker on resting electrocardiogram (ECG); h) unstable angina; i) myocardial infarction.

Figure 1 shows a flowchart of the sample. Initially, 186 older adults were contacted. Forty-seven were not included due age, comorbidities according to criteria and MEEM score < 18. Frailty screening was applied in 139 individuals and 99 were excluded due frailty status or not interest in study. Thus, 40 were considered eligible prefrail. They were randomized into two groups that included 20 subjects in the multicomponent training intervention group

(MulTI), who participated in a multicomponent physical exercise protocol and 20 participants in the control group (CG), which was oriented to follow their own habitual daily activities. After data analysis and exclusion by withdrew participation (desistance) and signal artefacts, the final sample was composed by 21 subjects: MulTI (n = 12) and CG (n = 9) (see Figure 1).

Figure 1 - Flowchart of the final sample



3.2.3. Randomization process

After the first assessment, the participants were randomly distributed by software Random Allocation into blocks of eight subjects. According to the randomization sequence, each participant corresponded to an opaque and sealed envelope, numbered in order, containing a card indicating which group the individual would be inserted (MulTI or CG). The entire randomization process was performed by a researcher who had no link to the study (J.H.A.). The envelopes were opened after the first evaluation and the researchers were blinded about the allocation of the participants.

The assessments were performed in two distinct times: 1) baseline (initial assessment) and post-intervention (immediately after the conclusion of the 16-week multicomponent intervention).

3.2.4. Anamnesis

All participants were submitted to a structured interview. Demographic data (age, ethnicity and sex), educational level, comorbidities, medicine use were collected.

3.2.5. Functional Measures

Six-Minute Walk Test (6MWT)

The 6MWT is used to assess the submaximal exercise capacity of individuals from the longest distance walked in six minutes (ATS, 2002). Data was collected regarding the walk distance (WD) by volunteers and scores of dyspnea and fatigue of lower limbs by the 0-10 scale of Borg (Borg, 1998), which was previously explained to the patient, being 0 no symptoms and 10 the maximum symptom perceived by the same. The recommendations for the 6MWT were followed according to the American Thoracic Society (ATS, 2002).

Gait Speed

Gait speed was calculated considering the 4.6m walk test (Fried et al., 2001). Data was collected related to the time wasted to walk a distance of 4.6m. To perform this test, the volunteers were instructed to walk in their habitual speed. The 4.6m test was performed three times and a mean value was calculated. Gait speed value was derived from the physics formula (distance by time) and was represented in meters/seconds (m/s).

3.2.6. Procedures and experimental protocol for ANS assessment

Initially, the volunteers were instructed to remain in supine position for 10 minutes in order to stabilize cardiovascular variables and to conduct the calibration procedure. ECG, blood pressure (BP) and breathing recordings were collected for 15 minutes in supine position. Then, the volunteers were instructed to actively change to orthostatic position, in which they remained for 15 minutes. Previous instructions prior to the experiment were given related to not to ingest caffeine or alcohol, not to perform moderate or heavy exercise on the day before participation and have a regular meal.

The experiments were conducted in a climate-controlled (22-23°C) room with relative air humidity of 40-60% always in the morning in order to minimize circadian cycle effects.

3.2.7. Signal acquisition

The ECG signal was collected by a bioamplifier (BioAmp Power Lab - Ad Instruments, Australia) with electrodes placed on the MC5 lead, and respiratory movements were captured by a respiratory belt (Marazza, Monza, Italy). The arterial BP waves were obtained by a plethysmography arterial pressure device (Finometer PRO, Finapress Medical Systems, The Netherlands), with a cuff placed on the distal extremity of the right middle finger. This hand was kept close to the volunteer's heart with the help of a sling, which fixed the volunteer's arm to his chest throughout the experiment. The signal acquisition frequency was sampled at 1000 Hz.

The extraction of beat-to-beat variability series was carried out according to previous descriptions (Faes, Nollo, & Porta, 2013). After extraction of the series, 256-points sequences with the greatest stability were chosen for both positons (Task Force, 1996).

3.2.8. Data analysis

Baroreflex Sensitivity

Baroreflex was evaluated by phase, coherence (K^2), and gain (α). Baroreflex was calculated by cross spectral analysis using a bivariate autoregressive model (Porta, Aletti, Vallais, & Baselli, 2009). The phase is computed as the phase of the cross-spectrum from BP to RRi and represents the delay between the change in BP and the subsequent change in RRi, measured in radians. Coherence (K^2) was used to estimate the strength of the coupling between RRi and BP. The squared coherence is computed as the ratio of the squared modulus of the cross-spectrum to the product of the power spectra. In this study, phase and coherence were sampled at the frequency of vasomotor oscillations (Mayer waves) at the low frequency band (LF), which oscillates between 0.04-0.15 Hz and is related to the sympathetic predominance (Pagani et al., 1986; Task Force, 1996). Gain in the LF band was calculated as the square root of the ratio of the LF power of the RRi series to that of the BP series (Nollo et al., 2001) and characterizes the relation between BP and RRi.

Sample Entropy (SampEn)

Entropy is a measure of the information needed to predict the future state of a system. It provides a characterization of the dynamic of a signal, the greater the dynamics, the greater the entropy and the less predictable the system (Lipsitz, & Goldberger, 1992; Lipsitz, 2002). Entropy is related to the randomness and regularity of the system (Pincus, 1991).

Sample entropy (SampEn) (Richman, & Moorman, 2000) is a complexity measure used to quantify regularity of time series, especially short and noisy sequences. It is a measure that monitors how much a set of patterns that are close together for a few observations. Lower values for SampEn indicate regularity and predictability. In this study, were computed with $m = 2$, $r = 0.2$ times the standard deviation of the signal, and $N = 256$. M represents the length of the vector (patterns) to be compared; r represents the radius within which the comparison between the vectors are achieved (similarity criteria).

3.2.9. Intervention Protocol

The multicomponent exercise intervention was designed considering the recommendations proposed by American College of Sports Medicine (ACSM, 2009). The protocol consisted on aerobic, muscle strength, flexibility, and balance exercises. It was applied during 16 weeks, for three non-consecutive days, with 60-minute sessions. The sessions were composed by: a) 10 minutes of warm-up (light walk); b) 20 minutes of aerobic exercises; c) 10 minutes of balance exercise; d) 15 minutes of resistance exercises; e) 5 minutes of warm-down. Details concerning exercise type, intensity and progression are described in table 1.

Table 1 - Structure of the protocol intervention of the 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 started at 45% HRR in the first two weeks and increased by 5% every two weeks until reaching 80% HRR. During the training sessions, the THR was 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 protection strategies (ankle, hip, and step).	If necessary, a physiotherapist manually induced a slight unbalance.	The progression of these exercises was 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), 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; strengthening for the upper limbs; 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 followed the same criterion of progression mentioned in the familiarization (through the Borg CR-10 Scale).
Warm-down (5 minutes)	Breathing exercises and stretching for global muscles groups.	30-60s of static stretching	Until reaching resting HR and BP

Before the beginning of the intervention, all volunteers of the IG were invited to participate of three sessions in non-consecutive days for familiarization process and determination of resistance training load. The participants should perform one set of 8 repetitions without additional weight and report the level of effort according to the Borg CR-10 scale (Borg, 1998). If the score was into 5 to 8, the repetitions as well as the load would be maintained for the first two weeks of the resistance training. If below 5, the number of repetitions would be progressively increased until 12. If the volunteer reported a score below 5 even after the 12 repetitions performed, a 0.5-kg load would be added to the involved limb or segment (Giné-Garriga, Roqué-Fíguls, Coll-Planas, Sitjà-Rabert, & Salvà, 2014). This procedure was performed individually for each exercise: (i) sit to stand from the chair; (ii) strengthening exercises for the upper limbs; (iii) calf exercises; (iv) lunges; (v) step up and step down. Halters and a special waistcoat (vest) with large pockets (where ankle weights could be inserted) were used to facilitate the exercise execution and load increase.

For aerobic component, the training started at 45% of heart rate reserve (HRR) in the first two weeks and increased by 5% every two weeks until reaching 80% HRR (Toraman & Ayceman, 2005). Participants used a cardiac frequency monitor (Polar Polar® S810i) during walking on the ground or on the treadmill.

The progression for balance component was performed concerning 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) (ACSM, 2009), changes in the direction and speed, and overload of muscular groups involved in the posture (walking on tiptoe, heel).

And related to flexibility, exercises were applied separately for global muscles groups during 30s to 60s.

3.2.10. Statistical analysis

Sample size was determined with previous pilot study through normal distribution table, considering gain (BRS) as main variable, standard error 0.30 and significance level of 5%. Thus, a total sample composed by at least 12 would be necessary.

The Shapiro-Wilk test was used to verify the normality of data distribution. A Student's paired t test was used to compare age, anthropometric characteristics (weight, stature, BMI) and number of comorbidities at baseline. A chi-square test was applied to compare sex.

A linear mixed model test was used in order to assess the effect of the training at the baseline and post-intervention, between MulTI and CG on cardiovascular variables in supine rest position, and on functional measures (6MWT walk distance and speed gait). Besides, the same test was used to assess the effect on postural maneuver separately for each group, considering assessments (baseline x post) and positions (supine x orthostatic).

The significance level established was 5%. Statistical analysis was performed using the software IBM SPSS Statistics, version 20.0 (Armonk, NY, USA, 2011).

3.3. Results

The volunteers' age, anthropometric, and clinical characteristics are presented in table 2. There was no difference in sex, age, weight, stature and number of comorbidities between the groups. There was significant difference for BMI ($P = 0.032$), and 6MWT walk distance ($P = 0.011$) between the groups.

Table 2 Age, anthropometric and clinical characteristics

	MulTI (*N* = 12)	CG (*N* = 9)	*P* value
Female gender, *N* (%)	10 (83.3)	5 (55.6)	0.163
Age (y)	77.00 ± 6.80	73.78 ± 6.28	0.281
Weight (kg)	76.26 ± 12.72	68.54 ± 8.69	0.135
Stature (cm)	154.83 ± 6.48	159.56 ± 5.90	0.102
BMI (kg/m^2)	31.95 ± 5.47	27.02 ± 3.74	**0.032**
Comorbidities	2.33 ± 1.30	2.44 ± 1.81	0.872
6MWT walk distance (m)	326.42 ± 64.42	401.00 ± 53.18	**0.011**

Notes: Values are expressed as mean ± standard deviation or total of individuals (percentile). y = years; BMI = body mass index; CG = control group; MulTI = multicomponent training intervention; 6MWT = 6-minute walk test.

Table 3 presents BRS and SampEn in rest supine position. In terms of BRS, there was no difference in any parameter. Concerning SampEn, despite groups there was a significant reduction in post assessment in comparison to baseline (*P* = 0.036).

Table 3 - SampEn and Baroreflex sensitivity in MulTI and CG in supine position

	MulTI		CG		*P*-value		
	Baseline	Post	Baseline	Post	Groups	Assessments	Interaction
SampEn	1.72 ± 0.58	1.30 ± 0.46	1.72 ± 0.38	1.32 ± 0.43	0.971	**0.036**	0.945
BRS							
Coherence	0.51 ± 0.12	0.36 ± 0.16	0.51 ± 0.17	0.55 ± 0.28	0.992	0.076	0.117
Phase (rad)	-1.10 ± 1.19	-1.76 ± 1.09	-1.16 ± 1.61	-0.81 ± 2.59	0.830	0.573	0.889
Gain (ms/mmHg)	5.03 ± 3.59	7.07 ± 4.00	3.47 ± 1.45	7.43 ± 5.84	0.521	0.239	0.727

Notes: Values are expressed as mean ± standard deviation. BRS = baroreflex sensitivity; CG = control group; MulTI: multicomponent training intervention; SampEn = Sample entropy; $^{*}P < 0.05$ in comparison to baseline (baseline > post);

The postural maneuver behavior of each group between assessments was reported in Tables 4 and 5. Thus, the effects of positions (supine x orthostatic) and assessments (baseline x post) were tested for each group considering BRS and SampEn. The CG did not present significant differences for position, assessment or interaction in BRS parameters. Nonetheless there was a reduction in post assessment related to baseline for SampEn (P = 0.008) (table 4).

The MulTI did not present any significant differences for BRS or SampEn values between position, assessments or interaction (table 5).

Table 4 - SampEn and Baroreflex Sensitivity in CG

	Baseline		Post		*P*-value		
	Supine	Orthostatic	Supine	Orthostatic	Position	Assessments	Interaction
SampEn	1.72 ± 0.38	1.75 ± 0.50	1.32 ± 0.43	1.06 ± 0.33	0.880	**0.008**	0.366
BRS							
Coherence	0.51 ± 0.17	0.50 ± 0.22	0.55 ± 0.28	0.58 ± 0.23	0.942	0.314	0.719
Phase (rad)	-1.16 ± 1.61	-1.77 ± 0.84	-0.81 ± 2.59	-1.34 ± 0.47	0.410	0.615	0.966
Gain (ms/mmHg)	3.47 ± 1.45	4.14 ± 2.70	7.43 ± 5.84	4.23 ± 2.99	0.684	0.932	0.082

Notes: Values are expressed as mean ± standard deviation. BRS = baroreflex sensitivity; SampEn = Sample entropy. $^{*}P < 0.05$ in comparison to baseline (baseline > post).

Table 5 - SampEn and Baroreflex Sensitivity in MulTI

	Baseline		Post		*P*-value		
	Supine	Orthostatic	Supine	Orthostatic	Position	Assessments	Interaction
SampEn	1.72 ± 0.58	1.53 ± 0.43	1.30 ± 0.46	1.36 ± 0.42	0.320	0.231	0.316
BRS							
Coherence	0.51 ± 0.12	0.49 ± 0.13	0.36 ± 0.16	0.46 ± 0.19	0.730	0.593	0.152
Phase (rad)	-1.10 ± 1.19	-1.87 ± 0.89	-1.76 ± 1.09	-1.49 ± 1.34	0.106	0.385	0.090
Gain (ms/mmHg)	5.03 ± 3.59	2.76 ± 1.99	7.07 ± 4.00	4.01 ± 4.65	0.133	0.449	0.713

Notes: Values are expressed as mean ± standard deviation. BRS = baroreflex sensitivity; MulTI = multicomponent training intervention; SampEn = Sample entropy

Considering the functional measures, there was a group effect (*P* = 0.019) for walk distance indicating the CG presented higher values in comparison to MulTI. Besides, for gait speed CG also presented higher values related to MulTI (*P* < 0.001) and in post assessment both groups presented a better performance (increase) in comparison to baseline (*P* = 0.001) (table 6).

Table 6 - Functional measures

	MulTI		CG		*P*-value		
	Baseline	Post	Baseline	Post	Groups	Assessments	Interaction
Functional measures							
Walk distance (6MWT) (m)	326.42 ± 64.42	323.50 ± 83.41	401.00 ± 53.18	414.00 ± 58.42	**0.019**	0.741	0.375
Gait speed (m/s)	0.74 ± 0.20	0.91 ± 0.16	1.05 ± 0.12	1.11 ± 0.14	**< 0.001**	**0.001**	0.183

Notes: Values are expressed as mean ± standard deviation. 6MWT = Six-minute walk test. $^{*}P < 0.05$ in comparison to baseline (post > baseline);

3.4. Discussion

Complexity is an elusive concept which has been inserted in biological and health researches once physiological systems are featured by a dynamic network of multiple interacting inputs between control mechanisms (Lipsitz, 2002). Physiological complexity is directly related to an adaptive capacity of the organism to ever-changing environment (Javorka et al., 2018). Thus, a healthy organism is characterized by presence of adaptability properties, which allows an effective coping and high functionality to respond to unpredictable stimuli and stresses of daily life (Goldberger et al., 2002; Lipsitz, 2002).

With aging process, the number and connectedness of these inputs is reduced, the output signal is simplified, which limits responses to stressors and features as a reduced physiological complexity (Lipsitz, 2002). As complexity falls further, it may impair functional capacity until cross frailty threshold (Lipsitz, 2002), resulting in evident vulnerability to adverse outcomes (Fried et al., 2001). Therefore, the greater the number of dysregulated physiological systems evolved, the stronger the likelihood of frailty development (Fried et al., 2009).

Previous studies identified impairment in cardiovascular control assessed by complexity measurements in frail older adults (Lipsitz, 2002; Chaves et al., 2008; Katayama, Dias, Silva, Virtuoso-Junior, & Marocolo, 2015). On the other hand, it is unclear if this impairment could be present in prefrail even in lesser proportion. It’s already known structural and functional alterations of noninvasive biomarkers of cardiovascular disease (CVD) such as level of carotid stenosis and wall thickness are prevalent in frail as well in prefrail individuals (Newman, et al., 2001). Also, it has already been demonstrated the negative influence of CVD in HR complexity (Chen et al., 2017). According to our findings, HR complexity is impaired in prefrail older adults even in rest supine condition, once a significant reduction was detected in post assessment in comparison to baseline despite the groups.

Once the network structure of physiological system enable alternate pathways to be used to achieve the same functions, even in adverse conditions as aging or disease, the organism may keep functional capacity if other neural components and their connections could compensate (Lipsitz, 2002). Nevertheless, in Frailty course probably there is a limited response repertoire due lesser interaction among the physiological systems, consequently the individual may present a too succinct/insufficient or exacerbated response. An example of this is the orthostatic hypotension described in frail individuals (Rockwood, Howlett, & Rockwood, 2012). Considering the baroreflex represents an interaction between control subsystems responsible by BP homeostasis (Di Rienzo, Parati, Radaelli, & Castiglioni, 2009), in agreement with previous study (Buto et al., 2019), our data suggests there is also an impairment in BRS in prefrail individuals.

The active postural maneuver is a functional task triggers some physiological alterations in cardiac contractility, vasoconstriction and HR by increase in sympathetic modulation and vagal withdrawn (Laitinen, Niskanen, Geelen, Länsimies, & Hartikainen, 2004; Monahan, 2007). Thus, it is expected the baroreflex mechanism acts by fast increase in HR and BP dropped until it restores to adequate levels. Concerning the cardiovascular dynamics response to postural maneuver, a healthy organism presents a decrease in gain of BRS (Laitinen, Niskanen, Geelen, Länsimies, & Hartikainen, 2004; Porta et al., 2013), increase in K^2 values (Porta et al., 2013), as well a decrease in HR complexity (Porta et al., 2014). Nonetheless, in frailty course it seems the mechanisms fail and the response is impaired, as well identified by performance of prefrail individuals in the present study once both groups did not respond adequately.

It remained unknown if complexity of cardiovascular control could be restored by any kind of intervention. To date, few studies have been developed aimed to investigate the effect of exercise intervention in cardiovascular complexity and BRS. Resistance training conducted among hypertensive older adults and young individuals promoted increase in HR complexity, whereas no change was identified in traditional measurements of HR (Heffernan, Fahs, Shinsako, Jae, & Fernhall, 2007; Millar, Levy, McGowan, McCartney, & MacDonald, 2013). Related to endurance training, it was demonstrated a 21-week progressive program was more effective in improvement (increase) of HR complexity in middle-aged women when compared to combined strength and endurance training or strength training alone (Karavirta et al., 2013). Similarly, 4-week endurance training in hypertensive middle-aged was capable to improve BRS while the strength training had the opposite effect (Collier et al., 2009).

As well the cardiovascular benefits from distinct exercise training are divergent, the underlying mechanisms are still uncertain. It has been suggested the physical exercise, specially endurance and resistance, could potentially restore at least partially the complex dynamics in physiological systems (Lipsitz, 2004) through the development of new network connections as well as a reorganization of information outflow (Lipsitz, 2002; Lipsitz, 2004) and consequently improve functional health.

Currently there are few intervention studies destined to physiological complexity outcomes. It has been assumed a protocol design which targets on multi-systems effects and treats risk factors to disability may have the greatest potential to restore healthy dynamics in biological systems (Lipsitz, 2004). In consonance, multicomponent exercise training has been considered as the most adequate intervention modality to frailty management especially in earlier stages (Dedeyne, Deschodt, Verschueren, Tournoy, & Gielen, 2017; Jadcazk, Makwana, Luscombe-Marsh, Visvanathan, & Schultz, 2018).

In this sense, it was hypothesized the multicomponent intervention protocol developed in the present study would be capable to improve the dynamics evolved in cardiovascular control. On the assumption that frailty is featured by multisystem dysregulation (Fried et al., 2009), it was thought a broad approach could mutually affect multiple physiological “gears” and restore their interaction, reflecting in HR complexity as well BRS. Nonetheless, our findings indicated this intervention was not capable to improve none of these parameters. It is possible the protocol design (load, duration and/or progression) may have not been the most adequate.

Some authors argue that although an intuitive rationality guide to multicomponent approaches, the complex systems theory suggests the modification of a single component of a system may contribute to global (holistic) effects on system behavior (Manor & Lipsitz, 2013). This seems to be consistent with theoretical basis which considers the frailty progression as dependent at least one abnormal system to be capable to trigger a downward spiraling and affect other healthy functional systems until achieve a whole dysregulated state (Fried et al., 2009).

Related to the functional measures, there was no effect of multicomponent training in walk distance in prefrail individuals. At baseline and even post intervention, CG presented better performance (higher walk distance) in comparison to MulTI. These findings are in consonance with the absence of effect from intervention to the other cardiovascular control measures. It was probably due the low aerobic load developed in the multicomponent intervention (60 min/week), which might not be enough to promote benefits. According to ACSM (2009), it has been suggested at least 150 min/week of moderate-intensity.

Besides gait speed has been considered as consistent predictor of adverse outcomes in community-dwelling older adults (van Kan et al., 2009) and as prognostic predictive for all-cause mortality in older cardiovascular disease patients (Kamiya et al., 2018), similarly complexity indexes proved prognostic value in myocardial infarction (Huikuri, Perkiömäki, Maestri, & Pinna, 2009). Thus, the combined usage of metrics to quantify complexity and functional measurements seems to contribute to the recommendations designated to specific programs for prefrail individuals as well could be potential method of risk stratification to them (Walston et al., 2006; van Kan et al., 2009).

3.5. Conclusion

Prefrail individuals demonstrated a reduction in HR complexity in rest condition, which confirms impairment in ANS related to cardiovascular control even in intermediate stage of Frailty. Related to postural maneuver they did not present the expected response, suggesting a difficult to deal with provocative tasks which affect homeostasis. Besides, 16-week multicomponent exercise training was not capable to improve HR complexity and BRS. Nonetheless, to not training seems to impair even more the dynamics evolved in cardiovascular control in prefrail older adults, identified by reduction in HR complexity.

Frailty management is challenger, once it presents specificities related to wide and multidirectional physiological features. In this sense, the earliest identification of systemic deficits through sensitive tools may help in development of effective interventions targeted to prefrail individuals. Future studies should be conducted testing the efficacy of different types of training on cardiovascular dynamics in large sample.

3.6. Limitations

The cardiopulmonary exercise testing which is considered as gold standard tool for determination of maximal oxygen uptake (VO_2 max) was not performed to assess aerobic capacity.

3.7. Competing interests

None declared.

3.8. Author contributions

M.S.S.B. and A.M.C.T. were responsible for conception and design of the study. All authors contributed to the acquisition, analysis, interpretation of data, and drafted or revised it critically for intellectual content. All the authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

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4. CONSIDERAÇÕES FINAIS E DESDOBRAMENTOS FUTUROS

Os estudos desenvolvidos contribuíram com informações a respeito de aspectos ainda incertos acerca do controle cardiovascular, e de possíveis mecanismos relacionados ao comportamento dinâmico da FC em idosos pré-frágeis, bem como dos efeitos de uma intervenção multicomponente sobre os mesmos.

Assim, a partir destes estudos, concluiu-se que uma intervenção multicomponente de 16 semanas não foi efetiva na melhora da modulação autonômica cardiovascular. No entanto, os achados indicaram que indivíduos pré-frágeis que não realizaram a intervenção apresentaram uma piora da complexidade da FC ao longo do tempo. Sugere-se, portanto, que o treinamento foi capaz de manter os níveis de complexidade da FC em idosos pré-frágeis que participaram da intervenção.

Dada à relevância da síndrome da Fragilidade e de seus desfechos negativos, é indispensável que esta condição de saúde seja reconhecida e possa ser parte de toda conduta clínica não somente correlata à geriatria. Além disso, o uso de medidas de complexidade pode ser uma importante ferramenta aliada às medidas tradicionais para o seguimento do estado de saúde dos idosos. Igualmente, espera-se que novas intervenções sejam estimuladas respeitando as especificidades relativas à Fragilidade, para que um adequado manejo seja conduzido e permita amplos benefícios para esta população vulnerável.

5. ATIVIDADES DESENVOLVIDAS DURANTE O DOUTORADO

Durante o período de realização do Doutorado (Março de 2015 a Fevereiro de 2019) foram desenvolvidas as seguintes atividades:

- Coorientação da aluna Luiza Campanharo Bezerra de Menezes (Iniciação Científica na Universidade Federal de São Carlos com bolsa PIBIC).
- Orientação da aluna Caroline Bertholdo Dalarmi (Especialização de Fisioterapia em Neurologia pelo Instituto Israelita de Ensino e Pesquisa Albert Einstein).
- Orientação da aluna Priscila Moreira Pedreira Kosaka (Especialização de Fisioterapia Geriátrica pela Universidade Federal de São Carlos)
- Participação do Projeto de Extensão "Revitalização Geriátrica: Novos Desafios"
- Participação no Projeto de Doutorado de Dança Circular com cuidadoras de idosos com Doença de Alzheimer.
- Participação da Organização da Oficina de Cuidadores de idosos com Doença de Alzheimer.
- Participação e elaboração do 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* (em fase de análise).
- Elaboração do artigo "Effectiveness of complementary therapies on functional capacity and daily life activity of frail and pre-frail elderly: a systematic review of randomized controlled trials". (em fase final para submissão).
- Autora na publicação "Baroreflex Sensitivity in Frailty Syndrome" no periódico *Brazilian Journal of Medical and Biological Research.*
- Coautora na publicação "Linear and nonlinear analysis of postural control in frailty syndrome" no periódico *Brazilian Journal of Physical Therapy.*
- Coautora na publicação "Effects of the Addition of a Dual Task to a Supervised Physical Exercise Program on Older Adults' Cognitive Performance" no periódico *Journal of Aging and Physical Activity.*
- Coautora na publicação "Impact of a dual task intervention on physical performance of older adults who practice physical exercise" no periódico *Revista Brasileira de Cineantropometria e Desempenho Humano.*

APÊNDICE A – TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

UNIVERSIDADE FEDERAL DE SÃO CARLOS
CENTRO DE CIÊNCIAS BIOLÓGICAS E DA SAÚDE
DEPARTAMENTO DE FISIOTERAPIA

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

DADOS DE IDENTIFICAÇÃO DO SUJEITO DA PESQUISA OU RESPONSÁVEL LEGAL

NOME:...

DOCUMENTO DE IDENTIDADE Nº: .... SEXO: M □ F □

DATA NASCIMENTO: ..../......../......

ENDEREÇO: .... Nº: …...

CIDADE: ....

TELEFONE: DDD (............)..................................

DADOS SOBRE A PESQUISA

Este estudo tem por objetivo avaliar o efeito de um treinamento multicomponente no funcionamento do coração, no equilíbrio e na força muscular de idosos em risco de fragilização. A pesquisa será realizada em idosos considerados pré-frágeis com idade igual ou acima de 65 anos e residentes no município de São Carlos-SP.

A prática de exercício físico faz bem para a saúde e pode ajudar a combater a fragilização. O (a) senhor (a) foi convidado (a) a participar desta pesquisa como voluntário (a) e haverá um sorteio para saber em que grupo o (a) senhor (a) pertencerá: 1. Grupo intervenção, que fará exercício físico 3 vezes por semana em dias alternados, com duração de aproximadamente 1 hora pelo período de 16 semanas, e que tem por objetivo melhorar o alongamento, a força, o equilíbrio, o condicionamento cardíaco e a agilidade; 2. Grupo controle, que não participará dos exercícios, porém deve continuar a realização de suas atividades do dia-a-dia.

Antes do início do treinamento com exercícios, imediatamente após o seu término, e 6 semanas após a finalização, o (a) senhor (a) passará por algumas avaliações descritas abaixo e que deverão ser feitas em 3 dias diferentes.

Em uma delas o (a) senhor (a) responderá a um questionário. Nesta avaliação serão coletados dados referentes a idade, etnia, gênero, escolaridade, doenças associadas (diabetes, hipertensão, doenças cardiovasculares entre outras), uso de medicamentos, presença de problemas de audição e/ou visão, queixas de tontura , histórico de quedas nos últimos seis meses, atividades do dia-a-dia (escala de Lawton). Ainda serão avaliados a cognição (Mini Exame do Estado Mental - MEEM), sintomas depressivos (GDS-15) e composição corporal, ou seja, quantidade de músculo e gordura no corpo (DEXA). Para acompanhamento do seu nível de atividade física semanal, o fisioterapeuta fixará em sua coxa direita um pequeno aparelho (acelerômetro) com um adesivo. O (a) senhor (a) deverá usá-lo por sete dias.

O (a) senhor (a) também passará por três testes que avaliam sua capacidade funcional. No teste de caminhada de 6 minutos (TC6) o (a) senhor (a) será orientado (a) a caminhar em uma velocidade selecionada pelo senhor (a) durante 6 minutos. Neste teste seu coração será monitorado com uma cinta que registrará sua frequência cardíaca. Durante este teste o pesquisador acompanhará o nível de cansaço das pernas e falta de ar a cada minuto. No teste *Timed Up and Go* (TUG) o (a) senhor (a) deverá levantar-se de uma cadeira, caminhar na sua velocidade habitual por 3 metros e retornar, sentando-se novamente na cadeira. Além disso, o senhor executará uma bateria de testes chamada *Short Physical Performance Battery* (SPPB) por meio da qual serão avaliados o equilíbrio, a velocidade que o senhor caminha e a força da perna.

Ainda, para verificar como está seu equilíbrio e poder instruí-lo (a) quanto ao risco de quedas, o (a) senhor (a) fará uma avaliação sobre a plataforma de força (sensor que é fixado no chão) por meio da qual serão feitas quatro tarefas diferentes durante 30 segundos cada uma: 1. De pé, com os olhos abertos; 2. Levantar-se de uma cadeira e permanecer de pé com os olhos abertos; 3. De pé, com os olhos fechados; e 4. Tarefa envolvendo memória com olhos abertos. Cada um dos testes será realizado 3 vezes, com intervalo de duração entre eles de 1 minuto aproximadamente.

O (a) senhor (a) fará também um teste que consiste na avaliação da pressão arterial e da frequência cardíaca com o objetivo de verificar como está o funcionamento do seu coração e o controle do sistema nervoso. Será feito um eletrocardiograma (exame para verificar a atividade elétrica do seu coração), e os registros de sua frequência cardíaca e da pressão arterial. Para isso, será necessário que o senhor (a) fique em repouso deitado (a) de barriga para cima por 10 minutos e, após isso, o registro será realizado por 15 minutos na posição deitada e 15 minutos na posição em pé. Para este teste o (a) senhor (a) será orientado (a) para na véspera e no dia do teste não realizar exercícios vigorosos; não ingerir bebidas alcoólicas e estimulantes (chá, café, chocolate); alimentar-se bem e ter um bom período de sono (tempo e qualidade); fazer uma refeição leve até 2 horas antes do teste e vestir roupas e calçados (tênis) confortáveis.

Além dessas avaliações, o (a) senhor (a) será submetido (a) a avaliações da massa e força muscular. A avaliação da massa muscular será realizada utilizando o DEXA e o senhor (a) deverá utilizar roupas de algodão leve. Para mensurar a força dos músculos do joelho será utilizado um aparelho (dinamômetro isocinético). Neste aparelho o senhor realizará seis contrações de força máxima e outras 3 com força submáxima.

Em relação à entrevista com o questionário, o (a) senhor (a) pode sentir-se constrangido (a) em responder questões relacionadas a nível educacional. Dessa forma, o (a) senhor (a) pode negar-se a responder qualquer questão.

Todos os testes são considerados seguros, porém em alguns deles como no TC6, na realização da SPPB, do TUG e na avaliação do equilíbrio na plataforma de força existe o risco do senhor (a) se desequilibrar e cair. Este risco também existe durante a participação do grupo intervenção, já que envolve a prática de exercícios, assim como o risco de se sentir mal devido à prática de exercícios. No entanto, durante todos os testes assim como durante a prática dos exercícios, o (a) senhor (a) será acompanhado por um profissional capacitado e treinado, que estará próximo ao senhor (a), e caso seja necessário, ele intervirá para que a queda não ocorra. Ainda, durante o TC6 e a avaliação do coração o (a) senhor (a) poderá sentir também um pouco de tontura, vista embaçada ao se levantar assim como cansaço nas pernas e falta de ar ao se levantar ou caminhar. Este risco será minimizado, pois será realizada a monitorização contínua dos valores de pressão arterial e frequência cardíaca e identificado precocemente qualquer sinal de queda da pressão arterial com a mudança de posição, visto que o avaliador estará capacitado com o curso de Suporte Básico de Vida. Durante o teste de sentar e levantar e a avaliação da força dos músculos extensores do joelho o (a) senhor (a) poderá sentir um cansaço nas pernas. Caso isso ocorra, o (a) senhor (a) tem a possibilidade de interromper a realização do teste sem penalização ou prejuízo algum. Todavia, essas avaliações serão supervisionadas por um avaliador experiente na condução desses testes.

Mesmo com todo o suporte, caso ocorram quedas que acarretem a incapacidade de locomoção ou qualquer outro episódio como os citados acima que ofereça risco à saúde, e que seja decorrente da sua participação na pesquisa tanto no momento da avaliação, quanto durante o treinamento, o profissional responsável pela mesma se compromete a comunicar o serviço para sua locomoção até o serviço de atendimento apropriado.

Ao colar a fita adesiva do acelerômetro em sua coxa, o (a) senhor (a) poderá sentir desconforto no local da aplicação, portanto o profissional responsável estará atento a este risco e a qualquer relato ou sinal de processo alérgico (vermelhidão, coceira, dor) a fita adesiva será removida. Ainda, o (a) senhor (a) receberá orientações quanto aos cuidados, e poderá realizar todas suas atividades com o aparelho, inclusive tomar banho de chuveiro normalmente sem precisar retirá-lo, evitando apenas entrar em piscinas ou banheiras.

Caso o (a) senhor (a) seja alocado no grupo intervenção, alguns sintomas como dor muscular e sensação de cansaço poderão ser relatados após as sessões de exercícios, porém são esperados e devem ser minimizados com as técnicas de relaxamento ao final das sessões, uma vez que o organismo do (a) senhor (a) não está acostumado à prática regular de exercício físico. É esperado que ao longo das sessões essas queixas se reduzam. Adicionalmente, serão dadas orientações contendo sugestões de práticas não-medicamentosas de alívio de dor como a colocação de gelo e elevação das pernas. Como a intervenção envolve exercício físico, para reduzir ainda mais os riscos relativos à prática dos mesmos, serão tomadas as seguintes medidas: a) o (a) senhor (a) realizará uma avaliação médica liberando-o para a realização de atividade física e esta avaliação será conduzida pela médica cardiologista e docente do Departamento de Medicina Meliza Goi Roscani; b) antes do início de todas as sessões o (a) senhor (a) será questionado sobre seu estado de saúde, sobre a realização de alimentação prévia e presença de dores; c) o treinamento será aplicado por profissionais formados, habilitados e capacitados em reconhecer os sinais e sintomas de intolerância ao exercício físico; d) o risco de quedas durante a intervenção também será minimizado uma vez que serão formados pequenos grupos de 6 idosos, permitindo que se realize os exercícios com um instrutor por perto.

O (a) senhor (a) realizará procedimentos de familiarização com os testes, pessoal técnico, equipamentos e materiais utilizados a fim de evitar qualquer ansiedade ou receio.

Caso o (a) senhor (a) seja participante do grupo controle, suas atividades diárias deverão ser mantidas. Finalmente, caso o programa de intervenção se mostre efetivo, o (a) senhor (a) será convidado a participar do mesmo.

Após a avaliação de seguimento o (a) senhor (a) receberá um calendário, que deverá ser preenchido nos seis meses seguintes no caso da ocorrência de queda (s). Uma vez ao mês, por meio de contato telefônico, vocês serão questionados quanto à ocorrência de quedas nos últimos trinta dias, e será reforçada a definição da mesma, assim como o preenchimento do calendário. Ao término de seis meses, este calendário será recolhido em visita à sua casa.

A entrevista e os testes, assim como o treinamento com exercícios, serão realizados em instalações adequadas e por profissional qualificado. Sua identidade será mantida em sigilo absoluto. Os testes e exercícios visam beneficiar a população idosa, permitindo que se consiga prevenir, identificar alterações relativas aos sistemas avaliados e alertar sobre o risco de fragilização.

Os dados coletados nas avaliações serão utilizados apenas para fins científicos com a máxima confidencialidade, e não serão cedidos a qualquer pessoa ou entidade alheia a pesquisa, sob nenhuma circunstância. O nome dos participantes não será divulgado. Caso sejam encontradas quaisquer alterações nos testes realizados, o (a) senhor (a) será comunicado e orientado a procurar pelo o serviço de saúde adequado para melhor investigação. Para isso, o pesquisador fornecerá uma carta de encaminhamento com os achados do teste.

Não está previsto nenhum tipo de ressarcimento financeiro pela sua participação na pesquisa. Não há despesas pessoais e benefícios próprios, como seguro de saúde ou de vida e compensação financeira, para o participante. O senhor (a) deverá se responsabilizar pelo deslocamento até o local da realização da pesquisa, entretanto, o (a) senhor (a) não terá gastos referentes ao transporte, uma vez que os indivíduos acima de 60 anos podem utilizar gratuitamente o serviço de transporte público da cidade de realização da pesquisa.

É garantida a liberdade de retirada do consentimento de participar do estudo em qualquer momento, sem que isso gere qualquer prejuízo ao voluntário.

Este termo foi elaborado em duas vias e o (a) sr (a) receberá uma via assinada pelo pesquisador, contendo os contatos dos pesquisadores e do Comitê de Ética e Pesquisa UFSCar. Em qualquer etapa do estudo, poderá ter acesso aos profissionais responsáveis pela pesquisa para esclarecimento de eventuais dúvidas. Seguem abaixo as informações.

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Comitê de Ética e Pesquisa em Seres Humanos UFSCar
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Acredito ter sido suficientemente informado a respeito do estudo "Efeitos de um programa de treinamento multicomponente na complexidade de sinais biológicos em idosos pré-frágeis”. Ficaram claros para mim quais são os propósitos do estudo, os procedimentos a serem realizados, as garantias de confidencialidade e esclarecimentos permanentes. Ficou claro também que minha participação é isenta de despesas. Concordo voluntariamente em participar deste estudo e poderei retirar meu consentimento a qualquer momento, sem que isso gere prejuízo para mim.

Local:_______________________________________ Data: ____/____/______

____

Assinatura do voluntário

Declaro que obtive de forma apropriada e voluntária o Consentimento Livre e Esclarecido da respectiva pessoa para a participação no estudo.

____

Assinatura do pesquisador

ANEXO A – PARECER DO COMITÊ DE ÉTICA EM PESQUISA E SAÚDE

UFSCAR - UNIVERSIDADE FEDERAL DE SÃO CARLOS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Efeitos do treinamento multicomponente na complexidade de sinais biológicos em idosos pré-frágeis

Pesquisador: Anielle Cristhine de Medeiros Takahashi

Área Temática:

Versão: 5

CAAE: 54503916.2.0000.5504

Instituição Proponente: Universidade Federal de São Carlos/UFSCar

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 1.800.231

Apresentação do Projeto:

Trata-se de um estudo experimental cego randomizado controlado, cujas avaliações serão realizadas em três momentos (pré-intervenção, pós-intervenção de 16 semanas e follow-up de 6 semanas de destreinamento).

Objetivo da Pesquisa:

O objetivo principal deste estudo será avaliar o efeito de um programa de exercício multicomponente de 16 semanas na complexidade das oscilações cardiovasculares e de controle postural, além da complexidade das flutuações do torque articular de idosos pré-frágeis. Como objetivos secundários os proponentes destacam :

1. Avaliar o efeito do treinamento e destreinamento sobre: • A capacidade funcional e mensurada pelos testes: Teste de Caminhada de 6 minutos (TC6); Short Physical Performance Battery (SPPB); Timed up and Go (TUG); teste de velocidade de marcha (Fried et al. 2001); • Ocorrência de quedas pós-treinamento (seis meses a partir do follow-up de seis semanas);• Atividade eletromiográfica dos músculos tibial anterior e porções medial e lateral do gastrocnêmio;• Força de preensão manual (handgrip);• Composição corporal, pela absortiometria de Raios-X de dupla energia (DEXA);• Transições entre os status da fragilidade; • Nível de atividade física e padrão de sedentarismo pela acelerometria triaxial.

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2. Verificar se existe correlação entre:• As medidas de complexidade dos diferentes sistemas avaliados e os testes de capacidade funcional;• A complexidade das oscilações do controle postural e ocorrência de quedas pós-treinamento; •A complexidade da oscilação postural e a atividade elétrica dos músculos tibial anterior e porções medial e lateral do gastrocnêmio.

Avaliação dos Riscos e Benefícios:

Em relação às perguntas, há risco de constrangimento em responder questões relacionadas ao nível educacional ou renda familiar. Em relação aos testes selecionados e a intervenção proposta, existe o risco de quedas, de sentir-se mal devido à prática de exercícios, bem como tontura, vertigem ao se levantar assim como fadiga de membros inferiores e dispnéia ao se levantar ou caminhar. No entanto tais riscos serão minimizados pela presença de um profissional capacitado e treinado, que estará próximo a ele, e caso seja necessário, intervirá para que a queda não ocorra. Além disso, será realizada a monitorização contínua dos valores de pressão arterial e frequência cardíaca e identificado precocemente qualquer sinal de hipotensão postural, visto que o avaliador estará capacitado com o curso de Suporte Básico de Vida. Em qualquer momento, o voluntário poderá interromper a realização do teste sem penalização ou prejuízo algum. Todavia, essas avaliações serão supervisionadas por um avaliador experiente na condução desses testes. Mesmo com todo o suporte, caso ocorram quedas que acarretem a incapacidade de locomoção ou qualquer outro episódio como os citados acima que ofereça risco à saúde, e que seja decorrente participação na pesquisa tanto no momento da avaliação, quanto durante o treinamento, o profissional responsável pela mesma se compromete a comunicar o serviço para o encaminhamento até o serviço de atendimento apropriado.

Os pesquisadores ainda indicam o risco de desconforto ao colar a fita adesiva do acelerômetro no terço médio da coxa, portanto o profissional responsável estará atento a este risco e qualquer relato ou sinal de processo alérgico (vermelhidão, coceira, dor) será critério para remoção do objeto. Ainda, o voluntário receberá orientações quanto ao cuidados, e poderá realizar todas as atividades com o aparelho, inclusive tomar banho de chuveiro normalmente sem precisar retirá-lo, evitando apenas imersão em piscinas ou banheiras. Caso o voluntário seja alocado no grupo intervenção, alguns sintomas como dor muscular e sensação de cansaço poderão ser relatados após as sessões de exercícios, porém são esperados e devem ser minimizados com as técnicas de relaxamento ao final das sessões. Adicionalmente, serão dadas orientações contendo sugestões de práticas não-medicamentosas de alívio de dor como a colocação de gelo e elevação dos membros inferiores.

Como a intervenção envolve exercício físico, os riscos são os relativos a prática dos mesmos, sendo que estes serão minimizados pelas seguintes medidas: a) todos os voluntários realizarão uma avaliação médica previa liberando o mesmo para a realização de atividade física, esta avaliação será conduzida pela médica cardiologista e docente do Departamento de Medicina Meliza Goi Roscani b) antes do início de todas as sessões os voluntários serão questionados sobre seu estado de saúde, sobre a realização de alimentação prévia e presença de dores, c) o treinamento será aplicado por profissionais formados habilitados e capacitados em reconhecer os sinais e sintomas de intolerância ao exercício físico, d) o risco de quedas durante a intervenção também será minimizado uma vez que serão formados pequenos grupos de 6 idosos, permitindo que se realize os exercícios com um instrutor por perto.
Em relação aos benefícios, não haverá compensação para participação na pesquisa. No entanto, os exercícios visam trazer benefícios para a população idosa, como prevenção e alertar sobre o risco de fragilização, além de identificação de alterações relativos aos sistemas avaliados. Sabe-se que a prática de exercício físico é benéfica para a saúde como um todo e pode ajudar na reversão do processo de fragilização. Caso sejam encontradas quaisquer alterações nos testes realizados, o voluntário será comunicado e orientado a procurar pelo o serviço de saúde adequado para melhor investigação. Para isso, o pesquisador fornecerá uma carta de encaminhamento com os achados do teste. Caso os resultados do programa de intervenção mostrarem-se efetivos, os(as) idosos(as) pré-frágeis do grupo controle receberão o convite para participação do programa de intervenção.

Comentários e Considerações sobre a Pesquisa:

O projeto encontra-se bem estruturado, claro e conciso. A pesquisa proposta tem relevância científica e social e respeita os preceitos éticos estabelecidos pela Resolução CNS 466/2012 e suas complementares.

Considerações sobre os Termos de apresentação obrigatória:

Foram anexados os seguintes termos de apresentação obrigatória:

- Folha de rosto
- Termo de consentimento
- Projeto - novo
- Informações básicas do Projeto de pesquisa
- Autorização do local da pesquisa (Unidade Saúde Escola)
- Ofício ao Relator, respondendo e esclarecendo mudanças no projeto básico.

O Termo de Consentimento Livre e Esclarecido (TCLE) está adequado. Apresenta linguagem simples e adequada, permitindo boa compreensão dos procedimentos da pesquisa, além de informar a possibilidade de inclusão em diferentes grupos da pesquisa, seus possíveis riscos, desconfortos e benefícios, providências e cautelas para se evitar danos, participação voluntário e a liberdade em recusar-se a participar da pesquisa, garantia de sigilo e privacidade.

Conclusões ou Pendências e Lista de Inadequações:

Projeto adequado.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Recurso do Parecer	recurso.pdf	05/10/2016 11:56:57		Aceito
Recurso Anexado pelo Pesquisador	Oficio_ao_parecerista.pdf	05/10/2016 11:56:18	Ana Claudia Silva Farche	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_submetido_05_10_2016.pdf	05/10/2016 11:55:35	Ana Claudia Silva Farche	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_submetido_05_10_2016.pdf	05/10/2016 11:55:16	Ana Claudia Silva Farche	Aceito
Recurso do Parecer	recurso.pdf	09/08/2016 10:58:01		Aceito
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_662495.pdf	25/06/2016 09:16:32		Aceito
Outros	Aprovacao_USE.pdf	09/05/2016 18:04:08	Ana Claudia Silva Farche	Aceito
Outros	Declaracao_linha_de_cuidado_USE.pdf	10/03/2016 12:05:54	Ana Claudia Silva Farche	Aceito
Folha de Rosto	Folha_de_rosto_assinada.pdf	10/03/2016 12:01:32	Ana Claudia Silva Farche	Aceito

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

UFSCAR - UNIVERSIDADE FEDERAL DE SÃO CARLOS

Plataforma Brasil

Continuação do Parecer: 1.800.231

SAO CARLOS, 31 de Outubro de 2016

Assinado por:
Ricardo Carneiro Borra
(Coordenador)

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