UNIVERSIDADE FEDERAL DE UBERLÂNDIA
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FACULDADE DE MEDICINA

EFEITOS DOS EXERCÍCIOS FÍSICOS NA REATIVIDADE AO ESTRESSE E FATORES QUE INFLUENCIAM AS RESPOSTAS AO TREINAMENTO FÍSICOS EM MULHERES APÓS A MENOPAUSA: HIPERTENSÃO, ISOFLAVONAS E ANTI-HIPERTENSIVOS

IGOR MORAES MARIANO

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EFEITOS DOS EXERCÍCIOS FÍSICOS NA REATIVIDADE AO ESTRESSE E FATORES QUE INFLUENCIAM AS RESPOSTAS AO TREINAMENTO FÍSICOS EM MULHERES APÓS A MENOPAUSA: HIPERTENSÃO, ISOFLAVONAS E ANTI-HIPERTENSIVOS

Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para a obtenção do título de Doutor em Ciências da Saúde.

Área de concentração: Ciências da Saúde.

Orientador: Dr. Guilherme Morais Puga

Coorientadora: Dr. Paula Aver Bretanha Ribeiro

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Reuniu-se em web conferência pela plataforma Mconf-RNP, em conformidade com a PORTARIA Nº 36, DE 19 DE MARÇO DE 2020 da COORDENAÇÃO DE APERFEIÇOAMENTO DE PESSOAL DE NÍVEL SUPERIOR - CAPES, pela Universidade Federal de Uberlândia, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Ciências da Saúde, assim composta: Kátia De Angelis Lobo D'Avila (UNIFESP), Raphael Mendes Ritti Dias (Universidade Nove de Julho), Fábio Lera Orsatti (UFTM), Eimear Bernadette Dolan (USP) e Guilherme Morais Puga (UFU) orientador do candidato.

Iniciando os trabalhos o presidente da mesa, Dr. Guilherme Morais Puga, apresentou a Comissão Examinadora e o candidato, agradeceu a presença do público, e concedeu ao Discente a palavra para a exposição do seu trabalho. A duração da apresentação do Discente e o tempo de arguição e resposta foram conforme as normas do Programa.

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Resumo

Introdução: Mulheres após a menopausa fazem parte dos grupos de risco de incidência de doenças cardiovasculares. Uma das estratégias para prevenir e tratar essas doenças é o exercício físico. Contudo, não se sabe se os diferentes anti-hipertensivos podem afetar as respostas crônicas ao exercício físico. Além disso, não se sabe se estas respostas se mantem em situações de estresse após exercícios físicos de forma aguda ou crônica. **Objetivo**: Investigar as repostas cardiovasculares aos exercícios físicos em situações cotidianas e sob estresse, com foco em mulheres após a menopausa. **Métodos**: O presente trabalho será apresentado em formato de seis artigos científicos. Os textos foram organizados em três capítulos com dois estudos cada: Capítulo 1) discorre sobre as diferenças entre mulheres após a menopausa normotensas e hipertensas nas respostas crônicas ao exercício físico combinado; Capítulo 2) discorre sobre os efeitos de fitoestrogênios e anti-hipertensivos nas respostas cardiovasculares ao exercício físico crônico em mulheres após a menopausa; e Capítulo 3) discorre sobre os efeitos agudos e crônicos do exercício físico nos picos hipertensivos sob estresse. **Resultados**: Dentre os principais resultados destacamos: 1) o exercício físico combinado pode diminuir a pressão arterial e melhorar a modulação da frequência cardíaca de mulheres na pós-menopausa, independentemente da presença de hipertensão; 2) a suplementação com isoflavonas não promove efeitos adicionais ao exercício físico na variabilidade de frequência cardíaca de mulheres após a menopausa; 3) usuários de bloqueadores do receptor de angiotensina tem respostas favoráveis mais pronunciadas ao treinamento físico combinado na PA sistólica de vigília, enquanto as usuárias de β-bloqueadores apresentam respostas mais evidentes na variabilidade da pressão arterial; 4) A reatividade da pressão arterial não difere entre usuárias de bloqueadores do receptor de angiotensina e β-bloqueadores após treinamento exercício; e 5) tanto uma única sessão, quanto o treinamento com exercícios físicos, reduzem a reatividade da PA ao estresse. **Conclusões**: O exercício físico é uma estratégia eficaz para promover a saúde cardiovascular, tanto em repouso quanto sob situações de estresse, independente da presença de hipertensão ou do uso de isoflavonas, β-bloqueadores ou bloqueadores do receptor de angiotensina.

Palavras-chave: Hipertensão, Exercício, Menopausa, Pressão arterial, Variabilidade de frequência cardíaca, Anti-hipertensivos, Estresse.

Abstract

Introduction: Postmenopausal women are at risk for cardiovascular disease. One of the strategies to prevent and treat these diseases is physical exercise. However, it is not known whether the different antihypertensive drugs can affect chronic responses to physical exercise. Furthermore, it is not known whether these responses remain in stressful situations after acute or chronic physical exercise. **Objective**: To investigate cardiovascular responses to physical exercise in daily and stressful situations, focusing on women after menopause. **Methods**: The present work will be presented in the format of six scientific articles. The texts were organized into three chapters with two studies each: Chapter 1) discusses the differences between normotensive and hypertensive women after menopause in chronic responses to combined physical exercise; Chapter 2) discusses the effects of phytoestrogens and antihypertensives on cardiovascular responses to chronic physical exercise in women after menopause; and Chapter 3) discusses the acute and chronic effects of physical exercise on hypertensive peaks under stress. **Results**: Among the main results, we highlight: 1) combined physical exercise can decrease blood pressure and improve heart rate modulation in postmenopausal women, regardless of the presence of hypertension; 2) supplementation with isoflavones does not promote additional effects to physical exercise on heart rate variability in post menopause women; 3) users of angiotensin receptor blockers have more pronounced favorable responses to combined physical training in waking systolic BP, while users of β-blockers have more evident responses in blood pressure variability; 4) Blood pressure reactivity does not differ between users of angiotensin receptor blockers and β-blockers after physical exercise training; and 5) both a single session and physical exercise training reduce BP reactivity to stress. **Conclusions**: Physical exercise is an effective strategy to promote cardiovascular health, both at rest and under stress, regardless of the presence of hypertension or the use of isoflavones, β-blockers or angiotensin receptor blockers.

Key Words: Hypertension, Exercise, Menopause, Blood pressure, Heart rate variability, Antihypertensives, Stress.

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LISTA DE ABREVIATURAS E SIGLAS

ARV	Variabilidade real média ponderada para o intervalo de tempo entre leituras
HF	Alta frequência
LF	Baixa frequência
PA	Pressão arterial
pNN50	Porcentagem de pares de batimentos adjacentes diferindo por mais de 50ms
RMSSD	Raiz quadrada da média da soma dos quadrados das diferenças entre intervalos adjacentes
SD1	Eixo transversal da dispersão elíptica dos dados
SD2	Eixo longitudinal da dispersão elíptica dos dados
SD24	Desvio padrão de 24h
SDdn	Desvios médios ponderados pela duração do intervalo diurno e noturno
SDNN	Desvio padrão de todos os intervalos de batimentos normais

LIST OF ABBREVIATIONS AND ACRONYMS

1RM	One maximal repetition test
ABPM	Ambulatory blood pressure
ARB	Angiotensin receptor blockers users' group
ARV24 or ARV	Average real variability weighted for the time interval between readings
AUC	Area under the curve
BB	β-adrenergic blockers users' group
BP	Blood pressure
BPV	Blood pressure variability
CET	Combined exercise training
CON	Control group
DBP	Diastolic blood pressure
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
HT	Hypertensive
IPAQ	International Physical Activity Questionnaire
ISO	Isoflavone group
LF	Low frequency
MBP	Mean blood pressure
NT	Normotensive
PLA	Placebo group
pNN50	Percentage of pairs of adjacent RRi differing by more than 50 ms
RMSSD	Square root of the mean squared difference of successive R-R intervals

RRi	RR intervals
SBP	Systolic blood pressure
SD1	Transversal axis of the ellipse-like dispersion
SD2	Longitudinal axis of the ellipse-like dispersion
SD24	24-hour standard deviation
SDdn	Mean deviations weighted for the duration of the daytime and night-time
SDNN	Standard deviation of all normal R-R intervals

SUMÁRIO

INTRODUÇÃO

A menopausa é um ponto determinado retroativamente após 12 meses sem ciclo menstrual e o período após este evento é chamado de pós-menopausa (WARD; DENERIS, 2018). Mais detalhes sobre este período de transição podem ser encontrados na *Figura 1*. Neste sentido, a falência da função dos ovários na produção e liberação de estrogênio, que é característica desta fase, leva a diversas alterações fisiológicas (ABBAS et al., 2018; WARD; DENERIS, 2018). Estas alterações podem causar mudanças nos perfis autonômico (MERCURO et al., 2000), psicossocial (IGARASHI et al., 2000), lipídico e antropométrico, além de aumentar os níveis de estresse (IGARASHI et al., 2000) e a incidência de doenças cardiometabólicas, como a hipertensão arterial (ABBAS et al., 2018).

	Menarca					Menopausa (0)				
Estágio	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminologia	**Reprodutivo**				**Transição**		**Pós menopausa**			
					Perimenopausa					
Duração	Variável				Variável	1-3 anos	2 anos		3-6 anos	Tempo de vida restante
Principal critério (Ciclo menstrual)	Variável a regular	Regular	Regular	Mudança súbita de fluxo/duração	Ao menos 7 dias de diferença na duração de ciclos consecutivos	Intervalo >= 60 dias	Inexistente			

Figura 1 – *O sistema de estágios para o envelhecimento reprodutivo em mulheres. Adaptado de* (WARD; DENERIS, 2018)

A hipertensão arterial, por sua vez, é caracterizada pelo aumento sustentado da pressão arterial (PA) de repouso (BARROSO et al., 2021). Desta forma, é considerado hipertenso aquele que em repouso e na ausência de tratamento específico, tem PA cronicamente acima ou igual a 140 mmHg para a PA sistólica e/ou 90 mmHg para PA diastólica (BARROSO et al., 2021). Mais detalhes sobre as classificações de hipertensão podem ser encontrados na *Tabela 1*. Neste contexto, estudar doenças cardiovasculares é clinicamente relevante, pois são as principais causas de morbimortalidade no Brasil, com impacto socioeconômico elevado (BARROSO et al., 2021). Além disso, a incidência de doenças cardiovasculares é elevada após a menopausa quando comparadas aos homens de mesma idade e às mulheres antes da menopausa (DI GIOSIA et al., 2018; ZILBERMAN et al., 2015), o que torna este um importante grupo de estudo.

Tabela 1 – *Classificação da pressão arterial de acordo com medida casual ou de consultório.*

Classificação	PAS (mmHg)		PAD (mmHg)
Ótima	≤ 120	e	≤ 80
Normal	120-129	e/ou	80-84
Pré-hipertensão	130-139	e/ou	85-89
Hipertensão estágio 1	140-159	e/ou	90-99
Hipertensão estágio 2	160-179	e/ou	100-109
Hipertensão estágio 3	≥ 180	e/ou	≥ 110

PAS: Pressão arterial sistólica; PAD: Pressão arterial diastólica. Quando PAS e PAD se encontram em classificações diferentes deve-se considerar a mais alta. Adaptado de (BARROSO et al., 2021).

A prática de exercício físico regular por sua vez, é sugerida como uma estratégia fundamental para o tratamento da hipertensão arterial, por promover reajuste da PA em curto (CARVALHO et al., 2014; HALLIWILL et al., 2013) e longo prazo (CARVALHO et al., 2014; DE SOUSA et al., 2017; TIBANA et al., 2015), inclusive em mulheres hipertensas após a menopausa (LIN; LEE, 2018; SON et al., 2017a, 2017b). Além disso, os exercícios físicos ajudam a regular o balanço autonômico que é alterado nesta população (BHATI et al., 2019; SANDERCOCK; BROMLEY; BRODIE, 2005; VILLAFAINA et al., 2017). Desta forma, o treinamento com exercícios físicos pode contribuir para a prevenção de eventos cardiovasculares futuros, como infarto do miocárdio e acidente vascular encefálico (BUNDY et al., 2017), além de melhorar a inflamação sistêmica, o alto estresse oxidativo, a saúde óssea e os sintomas característicos da pós-menopausa (GIOLO et al., 2018; MENDOZA et al., 2016).

Entretanto, apesar dos resultados relevantes do exercício físico em hipertensos, não se sabe se o tipo de anti-hipertensivo utilizado interfere nestas respostas adaptativas, sendo que estes efeitos podem ser adicionais, independentes ou podem depender de alguma via saturada pelos fármacos. Portanto, compreender melhor os métodos de tratamento e prevenção de hipertensão arterial, assim como o papel adicional do exercício físico no controle cardiovascular é de grande relevância para a saúde pública, tanto no que se refere à melhoria na qualidade de vida, quanto aos gastos do sistema de saúde. Além disso, compreender as interações entre os tratamentos farmacológicos e não farmacológicos pode influenciar nas escolhas de combinações entre estes e garantir a efetividade de tratamento de forma individualizada.

FUNDAMENTAÇÃO TEÓRICA

MENOPAUSA E HIPERTENSÃO

A hipertensão arterial contribui para cerca de 50% das mortes por doenças cardiovasculares no Brasil e é associada ao risco de eventos cardiovasculares, acidentes cerebrais e doenças renais (BARROSO et al., 2021; BHAGANI; KAPIL; LOBO, 2018). Em relação à saúde da mulher, esta doença tem maior incidência a partir dos 50 anos (DI GIOSIA et al., 2018) e pode causar lesões de órgão alvo graves nesta população (MUIESAN et al., 2018). De forma geral, essa incidência pode ser explicada pela deficiência de estrogênio, que modula a PA principalmente através de ação endotelial (WASSERTHEIL-SMOLLER et al., 2000), elevando a produção de vasodilatadores como prostaciclinas e oxido nítrico (CARDOSO JUNIOR et al., 2007; ZANESCO; ZAROS, 2009). Este déficit hormonal somado aos altos índices de estresse (IGARASHI et al., 2000) e sedentarismo nesta população (WARD; DENERIS, 2018), induzem à grande incidência de doenças cardiovasculares como a hipertensão arterial (DI GIOSIA et al., 2018) e à pior modulação do controle autonômico cardiovascular (BROCKBANK et al., 2000; MERCURO et al., 2000; NEVES et al., 2007).

De forma mais específica, a redução de estrogênios pode contribuir para a disfunção endotelial e, portanto, para o aumento da PA. Neste sentido, o estradiol aumenta agudamente o cálcio intracelular, que ativa a óxido nítrico sintase endotelial, além de aumentar cronicamente a síntese dessa enzima, promovendo vasodilatação mediada por óxido nítrico (LIMA; WOFFORD; RECKELHOFF, 2012; YANES; RECKELHOFF, 2011). Além disso, o estradiol regula a enzima superóxido dismutase, que remove o superóxido que se ligaria ao óxido nítrico e o tornaria indisponível para a vasodilatação (LIMA; WOFFORD; RECKELHOFF, 2012; YANES; RECKELHOFF, 2011). Por fim, o estradiol é parcialmente metabolizado em 2-hidroxiestradiol e 2-metoxiestradiol, que estimulam a geração da prostaciclina, um vasodilatador, e reduzem a síntese de endotelina-1, um vasoconstritor (BARTON; MEYER, 2009). Por outro lado, o aumento dos androgênios após a menopausa estimula a síntese de ácido 20-hidroxieicosatetraenóico (um vasoconstritor) a partir da conversão do ácido araquidônico pelas ω-hidroxilases (YANES; RECKELHOFF, 2011). Além disso, em mulheres após a menopausa foi verificado menores níveis de epoxieicosotetraenóicos (substancias vasodilatadoras) que também advém do metabolismo do ácido araquidônico (YANES; RECKELHOFF, 2011). Desta forma, a redução dos níveis de estradiol e o aumento de androgênios geram um desbalanço na produção de vasodilatadores e vasoconstritores, causando aumento da PA.

Outro vasoconstritor que tem níveis elevados após a menopausa é a endotelina, mas o porquê de isso acontecer ainda não é claro. Uma possibilidade é de que a ativação do sistema renina-angiotensina por androgênios elevados na pós menopausa, aumente os níveis de angiotensina II, que estimula a síntese de preproendotelina (precursor da endotelina) (LIMA; WOFFORD; RECKELHOFF, 2012; YANES; RECKELHOFF, 2011). Outra possibilidade ainda pouco assertiva, é a ação direta do estradiol, visto que a terapia com este hormônio eleva os valores de endotelina (LIMA; WOFFORD; RECKELHOFF, 2012). Além disso, tanto a endotelina quanto a angiotensina II podem aumentar o estresse oxidativo, reduzir os níveis de óxido nítrico e, portanto, reduzir capacidade vasodilatadora (LIMA; WOFFORD; RECKELHOFF, 2012). Ainda em relação ao sistema renina-angiotensina, o estradiol parece regular a expressão de receptores de angiotensina II e da enzima conversora de angiotensina, reduzindo o efeito vasoconstritor desta via (BARTON; MEYER, 2009; LIMA; WOFFORD; RECKELHOFF, 2012; YANES; RECKELHOFF, 2011). Além disso, mulheres na pós-menopausa apresentam aumento na atividade da renina plasmática e da angiotensina II, comprometendo o manuseio renal de sódio (BARTON; MEYER, 2009; LIMA; WOFFORD; RECKELHOFF, 2012). Por fim, pode haver um componente genético que contribui para a hipertensão após a menopausa, visto que certos polimorfismos da renina estão associados à hipertensão em mulheres entre 40 e 70 anos, mas não em homens (LIMA; WOFFORD; RECKELHOFF, 2012; YANES; RECKELHOFF, 2011).

Outro fator importante, é que após menopausa há uma redistribuição da gordura corporal com aumento de gordura abdominal, que está associado a uma maior incidência de doenças cardiovasculares (LIMA; WOFFORD; RECKELHOFF, 2012; YANES; RECKELHOFF, 2011). Isso pode gerar aumento da inflamação sistêmica, medida através de marcadores pró-inflamatórios (e.g. proteína C reativa, fator de necrose tumoral alfa e interleucina 6), que favorecem o dano vascular nesta população (YANES; RECKELHOFF, 2011). Além disso, a gordura visceral está associada ao aumento da circulação de leptina, que estimula o sistema nervoso simpático através da ativação de receptores de melanocortina 4 no hipotálamo (YANES; RECKELHOFF, 2011). Essa ativação simpática é ainda reforçada pelo próprio ganho de peso, pelo envelhecimento e pelos níveis elevados de ansiedade e depressão nessa população (LIMA; WOFFORD; RECKELHOFF, 2012; YANES; RECKELHOFF, 2011). Desta forma o desbalanço autonômico em mulheres após a menopausa tem causa multifatorial e pode contribuir para o aumento da PA nesta população. Por fim, este balanço autonômico alterado, pode ser acentuado pela própria hipertensão arterial (HUIKURI et al., 1996; MARIANO et al.,

2020). Assim sendo, as alterações hormonais relacionadas à menopausa se conectam à hipertensão a partir de inúmeros mecanismos de ação que foram sintetizados na *figura 2*.

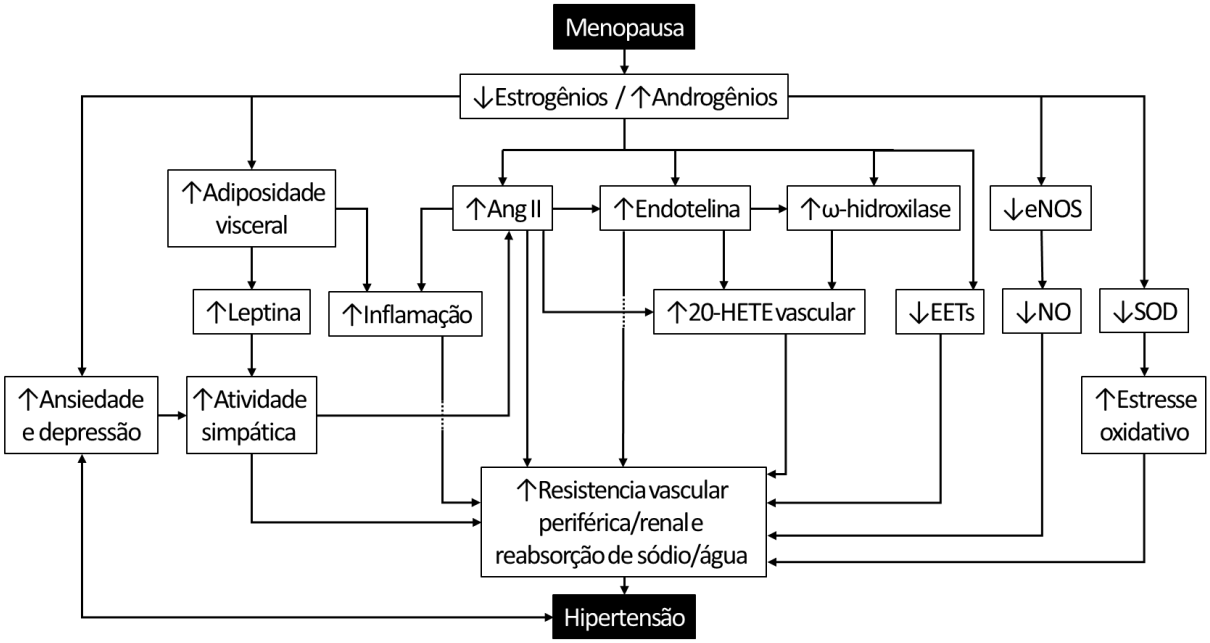

Figura 2 – M*ecanismos relacionados a menopausa que levam a hipertensão. Ang II: Angiotensina II; 20-HETE: Ácido 20-hidroxieicosatetraenóico (Vasoconstritor); EETs: Epoxieicosotetraenóicos (Vasodilatadores); eNOS: Enzima óxido nítrico sintase; NO: Oxido nítrico (Vasodilatador); SOD: Superóxido dismutase.*

TRATAMENTOS ANTI-HIPERTENSIVOS: FÁRMACOS E ESTILO DE VIDA

Dentre as medidas farmacológicas para o tratamento da hipertensão arterial, destacamos os bloqueadores de receptores de angiotensina II e os β-bloqueadores adrenérgicos por serem amplamente prescritos, além de agir por mecanismos díspares. Neste sentido, os bloqueadores de receptores de angiotensina agem de forma bastante sistêmica, bloqueando os receptores AT1 de Angiotensina II. Estes receptores estão presentes em diversos tecidos relacionados ao controle de PA, como: vasos, coração, rins, suprarrenais e nervos, com ação primária nos vasos periféricos (ABRAHAM; WHITE; WHITE, 2015). Estes medicamentos causam reduções na PA através de: **1)** relaxamento da vasculatura através do aumento de adenosina monofosfato cíclica e da diminuição da liberação de inositol trifosfato e de metabolitos do ácido araquidônico (ABRAHAM; WHITE; WHITE, 2015); **2)** redução da atividade simpática pela redução da liberação de catecolaminas (ABRAHAM; WHITE; WHITE, 2015); e **3)** redução da reabsorção de sódio e água nos rins pela diminuição da liberação/produção de aldosterona (BARROSO et al., 2021). Por outro lado, o mecanismo anti-hipertensivo dos β-bloqueadores pode envolver o

bloqueio de canais β-adrenérgicos em diversos tecidos, como: coração, rins e musculatura esquelética (BARROSO et al., 2021). Contudo, seus efeitos são mais centrais, causando diminuição do débito cardíaco, da frequência cardíaca, das catecolaminas nas sinapses e da secreção de renina, além de causar adaptação dos barorreceptores (BARROSO et al., 2021; LÓPEZ-SENDÓN et al., 2004).

Além dos fármacos, é recomendado em todos os níveis de hipertensão arterial, alterações no estilo de vida visando melhora e manutenção do resultado pressórico, dentre as quais destacamos a prática de exercícios físicos regulares (DE SOUSA et al., 2017). O exercício físico contribui com quedas na PA a curto (CARVALHO et al., 2014; HALLIWILL et al., 2013) e longo prazo (CARVALHO et al., 2014; DE SOUSA et al., 2017; TIBANA et al., 2015), na reatividade da PA ao estresse (HAMER; TAYLOR; STEPTOE, 2006; HUANG et al., 2013), além de colaborar no controle de diversos fatores, como: controle lipídico (GIOLO et al., 2018), função endotelial (SANTOS-PARKER; LAROCCA; SEALS, 2014), perfil oxidativo (ASHOR; LARA; SIERVO, 2017; GIOLO et al., 2018), regulação autonômica (BHATI et al., 2019; COTE et al., 2015; SANDERCOCK; BROMLEY; BRODIE, 2005; VILLAFAINA et al., 2017), sintomas do climatério (popularmente conhecidos como "sintomas da menopausa") (COSTA et al., 2017) e da saúde cardiovascular geral em mulheres hipertensas após a menopausa (LIN; LEE, 2018).

Neste sentido, diversos estudos (CORNELISSEN; SMART, 2013; NACI et al., 2018) demonstraram redução da PA após exercícios físicos em hipertensos, com resultados meta-analíticos similares aos dos tratamentos farmacológicos (ambos próximos a 9 mmHg de redução na PA sistólica, com diferença estimada em 0,18 mmHg com intervalo de confiança de -1,35 a 1,38 mmHg) (NACI et al., 2018). Contudo, a maioria dos estudos mostra eficácia dos exercícios aeróbicos (HACKAM et al., 2013; HECKSTEDEN; GRÜTTERS; MEYER, 2013) ou dos exercícios resistidos (CORNELISSEN; SMART, 2013; HERROD et al., 2018), mas poucos abordaram os resultados dos exercícios combinados (PEDRALLI et al., 2016; SON et al., 2017a). Apesar disso, os exercícios combinados apresentam resultados meta-analíticos promissores (alterações de -13,5 mmHg com intervalo de confiança de -16,5 a -10,5 mmHg) (NACI et al., 2018) e as diretrizes de hipertensão já recomendam que os hipertensos façam exercícios aeróbios complementados por exercícios resistidos (BARROSO et al., 2021; WHELTON et al., 2017). Quanto às características do exercício físico, os melhores resultados

pressóricos parecem se dar com exercícios físicos de intensidades moderadas a altas, em sessões de no mínimo 30 minutos e supervisionadas (CORNELISSEN; SMART, 2013).

Além disso, o exercício físico age sobre mecanismos de regulação da PA similares aos dos fármacos supracitados, causando: **1)** Aumento da sensibilidade barorreflexa (LIN; LEE, 2018); **2)** Melhora de *stiffness* arterial e vasodilatação dependentes do endotélio, associados a biodisponibilidade de oxido nítrico (causada por aumento de atividade enzimática e fosforilação de enzima oxido nítrico sintase, além de aumento nas concentrações disponíveis de nitrito, nitrato e óxidos de nitrogênio) (SON et al., 2017a); **3)** Redução da disfunção autonômica associada a hipertensão arterial, causando aumento do tônus vagal e diminuição do tônus simpático (BESNIER et al., 2017; LIN; LEE, 2018); **4)** Melhora da função endotelial induzida por aumento de produção e liberação de vasodilatadores, como acetilcolina e bradicinina (LIN; LEE, 2018) e; **5)** Melhoras na vasodilatação mediada por fluxo sanguíneo (VINET et al., 2018). Assim, as principais semelhanças entre os mecanismos de controle de PA dos fármacos supracitados e dos exercícios físicos estão exemplificadas na *tabela 2*:

Tabela 2 – M*ecanismos de regulação da pressão arterial similares entre fármacos e exercícios físicos.*

Fármacos	Mecanismos similares aos exercícios físicos
Bloqueadores de receptores de angiotensina II	Relaxamento da vasculatura/vasodilatação Redução da disfunção autonômica (aumento do sistema parassimpático e/ou diminuição do sistema simpático)
β-bloqueadores	Menor frequência cardíaca em repouso Maior sensibilidade barorreflexa

Portanto, dadas as semelhanças entre os mecanismos anti-hipertensivos dos medicamentos e dos exercícios físicos, surge a hipótese de que estas respostas poderiam interferir umas nas outras. Assim, a compreensão da interação das diferentes formas de tratamento da hipertensão arterial poderia influenciar na escolha da combinação entre medidas farmacológicas e de estilo de vida de forma a garantir a maior efetividade do tratamento. Com relação ao exercício físico crônico, uma metanálise (NACI et al., 2018) que envolveu 391 estudos sobre efeitos dos fármacos e dos exercícios físicos na PA, não encontrou nenhum estudo que verificasse a relação entre estas estratégias, o que evidencia esta lacuna de conhecimento na literatura. Além disso, essa metanálise reforça a importância do exercício físico em pacientes hipertensos, visto que os efeitos de redução pressórica das intervenções com exercícios físicos são similares aos dos fármacos anti-hipertensivos, como evidenciado na seção anterior.

Em contrapartida, as possíveis influências dos fármacos no controle pressórico associado aos exercícios físicos, têm sido demonstradas em ensaios com sessão única de exercícios físicos (BRITO et al., 2020; QUEIROZ et al., 2017; RAMIREZ-JIMENEZ et al., 2018b, 2018a). Nesse sentido, os bloqueadores de receptores de angiotensina parecem ter efeitos independentes, mas aditivos com exercício físico intenso (RAMIREZ-JIMENEZ et al., 2018a), causando reduções de PA mais acentuada que o exercício físico isolado (RAMIREZ-JIMENEZ et al., 2018b, 2018a). Por outro lado, os inibidores da enzima conversora de angiotensina parecem não alterar (QUEIROZ et al., 2017) ou até mesmo atenuar a hipotensão pós exercício físico (BRITO et al., 2020). Por fim, desconhecemos estudos que descrevam a influência de outras classes de medicamentos nas repostas pressóricas ao exercício físico, como β-bloqueadores, bloqueadores de canais de cálcio, α-bloqueadores, etc.

FERRAMENTAS DE AVALIAÇÃO CARDIOVASCULAR

Existem diversos métodos de avaliação dos valores de PA após fase ou sessão de exercícios físicos. O mais simples deles é a medida em repouso de PA, que tem importância clínica na prevenção/tratamento de hipertensão arterial, mas que limita a análise do comportamento da PA a apenas um momento (HINDERLITER; VOORA; VIERA, 2018). Assim, a monitorização ambulatorial de PA ganha destaque, já que a partir de um dispositivo portátil, fornece informações sobre os níveis de PA de 24h durante as atividades diárias usuais e durante o sono (HINDERLITER; VOORA; VIERA, 2018). Além disso, essa técnica permite um diagnóstico mais detalhado dos diferentes fenótipos de hipertensão, como: normotensão sustentada, hipertensão do avental branco, hipertensão mascarada, e hipertensão sustentada (HINDERLITER; VOORA; VIERA, 2018). Por fim, aumentos na pressão arterial sistólica média de 24h independentemente da pressão arterial de repouso no consultório, indicam maior risco de eventos cardiovasculares e acidentes vasculares cerebrais (PIPER et al., 2015).

Além disso, a medida ambulatorial de 24h pode fornecer informações sobre o comportamento temporal da PA (HANSEN et al., 2010), técnica conhecida como análise de variabilidade de PA. Essas variações podem ser entendidas como adaptações dos sistemas humoral, vascular e neural à estímulos internos e externos, e podem auxiliar no diagnóstico de alterações nos mecanismos de regulação da PA (PARATI et al., 2013, 2015). Apesar destes ajustes na pressão fazerem parte do controle homeostático do organismo, seu aumento sustentado está associado a um maior risco de eventos cardiovasculares e mortalidade (PARATI et al., 2013; STEVENS et al., 2016). Diversas são as estratégias para analisar as variações da

PA, mas no presente trabalho nos focaremos nas variações de curto prazo (dentro de 24h), entretanto, destacamos também a relevância clínica das análises de médio (alguns dias) e longo prazo (semanas, meses ou anos) (PARATI et al., 2015). Dessa forma, destacamos três parâmetros calculados a partir da medida ambulatorial da PA de 24h (PARATI et al., 2015): o desvio padrão de 24h (SD24), os desvios médios ponderados pela duração do intervalo diurno e noturno (SDdn), e a variabilidade real média ponderada para o intervalo de tempo entre leituras consecutivas (ARV). Todos estes parâmetros são calculados de forma simples, sem necessidade de equipamentos adicionais ao próprio aparelho de medida ambulatorial de 24h, e normalmente são calculadas a partir de aferições com intervalos de 15 a 20 minutos (PARATI et al., 2015).

Além das medidas clínicas tradicionais, a PA pode ser avaliada em resposta a situações de estresse através de diversos protocolos que envolvem estressores físicos e mentais (BALI; JAGGI, 2015). Desta forma é possível avaliar os picos hipertensivos dos indivíduos em situações estressantes como as que ocorrem no dia a dia, por exemplo no trânsito ou no trabalho. Neste sentido, a alta reatividade a estes protocolos pode indicar um maior risco de mortalidade cardiovascular (CARROLL et al., 2012), do desenvolvimento de hipertensão (MATTHEWS et al., 2003; MATTHEWS; WOODALL; ALLEN, 1993) e de ocorrência de eventos cardiovasculares futuros (BALI; JAGGI, 2015; TURNER et al., 2020). Além disso, há indícios de que a reatividade cardiovascular ao estresse é melhor preditora da massa ventricular esquerda e do desenvolvimento de hipertensão do que a própria PA de repouso (GEORGIADES et al., 1996; MATTHEWS; WOODALL; ALLEN, 1993; WOOD et al., 1984). Essas características adicionadas ao indício de que indivíduos hiper-responsivos em testes laboratoriais experimentam mais estresse diariamente (WIRTZ et al., 2008), sugerem que esses testes podem ser boas ferramentas de estratificação de risco cardiovascular. Quanto aos mecanismos responsáveis por estas respostas, níveis aumentados de catecolaminas (BRUMMETT et al., 2009; CHROUSOS, 2009; GERRA et al., 2001) e cortisol (FOLEY; KIRSCHBAUM, 2010; HERMAN et al., 2016; JUNG et al., 2017), além de alterações na rede neural (HERMANS et al., 2014; VAN OORT et al., 2017) e no sistema autonômico (APPELHANS; LUECKEN, 2006; CASTALDO et al., 2015; SMEETS, 2010; WALKER et al., 2017) podem explicar o aumento dos níveis de PA em situações estressantes (CHROUSOS, 2009; MYERS, 2017).

Neste momento é importante que fique clara a desambiguação entre os testes laboratoriais de estresse e o próprio exercício físico como ferramenta de estresse. Assim, o

exercício físico pode ser usado como causador de estresse caso haja padronização de um protocolo específico para isso, como ocorre com protocolos de *hand-grip* (SPRICK et al., 2020). Mas, os testes laboratoriais de estresse não se limitam a isso, e normalmente recorrem a protocolos de estresse psicossociais (BALI; JAGGI, 2015) por terem maior proximidade com as situações de estresse da vida moderna. Neste sentido, existem vários métodos de avaliação que envolvem estressores fisiológicos, ambientais, emocionais, cognitivos ou múltiplos, e que podem envolver avaliação social, falta de controle e imprevisibilidade (BALI; JAGGI, 2015). Mas, apesar de suas diferenças na metodologia e mecanismo de ação, os diferentes tipos de estressores parecem ter respostas semelhantes na reatividade de PA (BALI; JAGGI, 2015). Além disso, destacamos que durante os testes laboratoriais de estresse, pode-se avaliar diversos tipos de respostas do organismo (e.g. níveis de cortisol e catecolaminas, alterações do sistema autonômico, etc) (BALI; JAGGI, 2015), mas neste trabalho focaremos nas respostas da PA. Portanto, doravante nos referiremos a estes protocolos como "testes de reatividade de PA" ou de forma mais genérica como "testes laboratoriais de estresse".

Por fim, o balanço autonômico cardíaco pode ser avaliado de forma não invasiva através da análise da variabilidade da frequência cardíaca (SINGH et al., 1998; TASK FORCE OF THE EUROPEAN SOCIETY OF CARDIOLOGY THE NORTH AMERICAN SOCIETY OF PACING ELECTROPHYSIOLOGY, 1996). A redução desta variabilidade está relacionada a maior risco de arritmia e morte súbita, e uma maior variabilidade é relacionada a maior adaptabilidade ás situações (TASK FORCE OF THE EUROPEAN SOCIETY OF CARDIOLOGY THE NORTH AMERICAN SOCIETY OF PACING ELECTROPHYSIOLOGY, 1996). Além disso, essa ferramenta permite avaliar disfunções autonômicas, que são causas e consequências da hipertensão (DRENJANCEVIC et al., 2014). Por outro lado, para além de processos patológicos, é esperado que haja uma diminuição natural da variabilidade da frequência cardíaca com o envelhecimento (KUO et al., 1999). Em específico nas mulheres, este efeito é mais evidente após a menopausa (BROCKBANK et al., 2000; NEVES et al., 2007), já que nesta fase a redução dos níveis de estrogênio podem interferir na modulação autonômica cardiovascular (MERCURO et al., 2000). Além disso, há indícios de que os hormônios sexuais femininos influenciam a variabilidade de frequência cardíaca (BROCKBANK et al., 2000; YANG; MLČEK; KITTNAR, 2013), diminuindo parâmetros gerais (BROCKBANK et al., 2000) e de modulação parassimpática (VON HOLZEN et al., 2016). Por fim, algumas características específicas dessa população podem alterar estes parâmetros, tais como o uso de estrogênios exógenos (MAGRI et al., 2006; YANG; MLČEK;

KITTNAR, 2013) e presença de sintomas vasomotores (THURSTON; CHRISTIE; MATTHEWS, 2012). O treinamento de exercícios físicos por sua vez pode aumentar esta variabilidade (BHATI et al., 2019; PEARSON; SMART, 2018; SANDERCOCK; BROMLEY; BRODIE, 2005; VILLAFAINA et al., 2017), inclusive em populações com doenças cardiometabólicas (BESNIER et al., 2017).

Para que estes parâmetros sejam avaliados é necessário que se obtenha dados de frequência cardíaca com melhor qualidade e precisão possíveis. Tradicionalmente estes dados advém de eletrocardiogramas, mas com o desenvolvimento tecnológico podem ser obtidos com qualidade suficiente por dispositivos vestíveis de menor custo (DOBBS et al., 2019). Assim, a partir dos dados coletados, podemos avaliar a variação entre os batimentos cardíacos por diferentes perspectivas (também chamadas de domínios), como (TASK FORCE OF THE EUROPEAN SOCIETY OF CARDIOLOGY THE NORTH AMERICAN SOCIETY OF PACING ELECTROPHYSIOLOGY, 1996): **1)** Domínio do tempo, que avalia as alterações dos batimentos no decorrer do tempo; **2)** Domínio da frequência, que por meio de análise espectral, decompõe o sinal coletado e o avalia de acordo com a predominância de determinadas frequência de sinais que podem sugerir atuação de um dos braços do sistema autonômico; além de **3)** Análises não lineares, que utilizam de diferentes técnicas para análise de dispersão caótica de dados, por exemplo por meio do gráfico de Poincaré (TARVAINEN et al., 2014). Um esquema ilustrativo destes tipos de análise se encontra na figura a seguir:

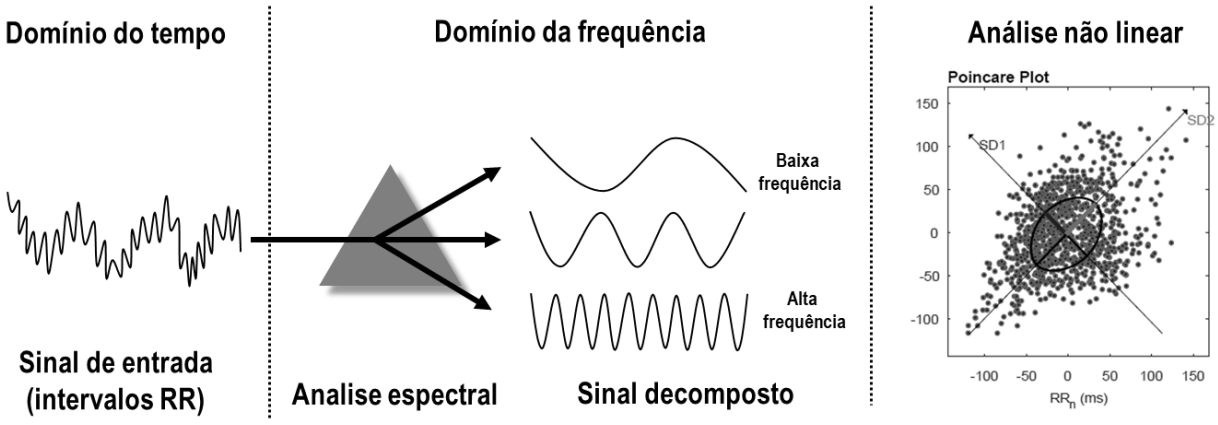

Figura 3 – *Domínios de análise de variabilidade da frequência cardíaca. Intervalo RR: tempo em milissegundos entre as deflexões R do eletrocardiograma.*

Dentre os índices do domínio do tempo, destacamos: o desvio padrão de todos os intervalos de batimentos normais registrados em um intervalo de tempo (SDNN), que é um

índice de variabilidade geral; a raiz quadrada da média da soma dos quadrados das diferenças entre os intervalos adjacentes (RMSSD), que é um índice de predomínio parassimpático; e a porcentagem de pares de batimentos adjacentes diferindo por mais de 50ms (pNN50), que também tem predomínio parassimpático. No domínio da frequência, os principais parâmetros são a baixa frequência (LF: 0,04–0,15 Hz) que representa ambos os ramos do sistema autonômico, e a alta frequência (HF: 0,15–0,40 Hz) que tem maior predomínio parassimpático. Além disso, o balanço simpático-vagal pode ser obtido através da razão das bandas de frequência (LF/HF), sendo que valores menores representam maior predomínio parassimpático (TASK FORCE OF THE EUROPEAN SOCIETY OF CARDIOLOGY THE NORTH AMERICAN SOCIETY OF PACING ELECTROPHYSIOLOGY, 1996). Para índices não lineares, o gráfico de Poincaré é um dos mais utilizados, no qual se examina os eixos transversal (SD1) e longitudinal (SD2) da dispersão elíptica dos dados. Sendo que o primeiro tem interpretação similar ao HF, o segundo ao LF, e sua razão (SD2/SD1) ao LF/HF.

CONSIDERAÇÕES GERAIS

O presente trabalho será apresentado em formato de seis artigos científicos nos próximos capítulos. Os textos foram organizados em três capítulos com dois estudos cada: **Capítulo 1)** discorre sobre as diferenças entre mulheres após a menopausa normotensas e hipertensas nas respostas ao exercício físico combinado; **Capítulo 2)** discorre sobre os efeitos de fitoestrogênios e anti-hipertensivos nas respostas cardiovasculares ao exercício físico em mulheres após a menopausa; e **Capítulo 3)** discorre sobre os efeitos do exercício físico nos picos hipertensivos sob estresse. Os dois estudos do **Capítulo 1** e o primeiro estudo do **Capítulo 2** foram realizados em colaboração a outros projetos vigentes no programa de pós-graduação entre os anos de 2015-2017. Estes geraram dúvidas acerca da influência dos anti-hipertensivos nas respostas ao exercício físico e deram origem ao segundo estudo apresentado no **Capítulo 2**. Entretanto, devido a pandemia de COVID-19, este estudo foi encerrado prematuramente e considerado um estudo piloto. Contudo, levantou o interesse e evidenciou lacunas existentes quanto aos efeitos dos exercícios físicos na reatividade ao estresse. Desta forma, este interesse originou os estudos do **Capítulo 3**, que discutem os efeitos meta-analíticos dos exercícios físicos agudos e crônicos nos picos hipertensivos sob estresse. As características gerais destes estudos estão apresentadas na tabela a seguir.

Tabela 3 – *Características gerais dos estudos.*

	Título adaptado ao português	Tipo de estudo	Exercício
Capítulo 1	**Comparação entre mulheres hipertensas e normotensas após a menopausa**		
Estudo 1	Variabilidade da pressão arterial ambulatorial e treinamento físico combinado: comparação entre mulheres hipertensas e normotensas após a menopausa	Quasi-experimento	Crônico
Estudo 2	Efeito do exercício combinado na variabilidade da frequência cardíaca em mulheres normotensas e hipertensas após a menopausa	Quasi-experimento	Crônico
Capítulo 2	**Efeitos de fitoestrogênios e anti-hipertensivos nas respostas cardiovasculares ao exercício**		
Estudo 3	Isoflavonas não promovem efeitos adicionais ao treinamento físico combinado na variabilidade da frequência cardíaca de mulheres após a menopausa: um estudo clínico, controlado, aleatorizado, duplo-cego	Ensaio clínico aleatorizado	Crônico
Estudo 4	Influência dos β-bloqueadores ou bloqueadores do receptor da angiotensina nas respostas cardiovasculares ao exercício em mulheres hipertensas na pós-menopausa: um estudo piloto	Quasi-experimento	Crônico
Capítulo 3	**Efeitos meta-analíticos do exercício nos picos hipertensivos sob estresse**		
Estudo 5	Uma única sessão de exercício reduz a pressão arterial induzida pelo estresse: uma revisão sistemática com metanálise	Metanálise	Agudo
Estudo 6	Pressão arterial induzida por estresse após treinamento físico: uma revisão sistemática com metanálise	Metanálise	Crônico

Frente ao que foi exposto, ao investigar as repostas cardiovasculares aos exercícios físicos em mulheres hipertensas e normotensas após a menopausa, em hipertensas sob efeito de diferentes anti-hipertensivos e os efeitos dos exercícios físicos na reatividade pressórica ao estresse, produzimos informações ainda não descritas na literatura. Estas informações, podem influenciar nas escolhas de diferentes características de exercício físico e de combinações entre tratamentos anti-hipertensivos farmacológicos e não farmacológicos de forma individualizada.

OBJETIVOS

O objetivo deste estudo foi investigar os efeitos dos exercícios físicos na reatividade ao estresse e fatores que alteram as repostas cardiovasculares aos exercícios físicos, com foco em mulheres após a menopausa.

OBJETIVOS ESPECÍFICOS

- Verificar e comparar os efeitos do exercício combinado na pressão arterial ambulatorial e sua variabilidade entre mulheres após a menopausa normotensas e hipertensas.
- Verificar e comparar os efeitos do exercício combinado na variabilidade de frequência cardíaca entre mulheres após a menopausa normotensas e hipertensas.
- Verificar se variabilidade de frequência cardíaca após o treinamento combinado são influenciadas pelo uso isoflavonas.
- Verificar se as respostas cardiovasculares após o treinamento combinado são influenciadas pelo uso de beta bloqueadores e bloqueadores de receptores de angiotensina II.
- Verificar os efeitos meta-analíticos de uma única sessão de exercício físico na reatividade da pressão arterial ao estresse.
- Verificar os efeitos meta-analíticos de uma fase de treinamento com exercício físico na reatividade da pressão arterial ao estresse.

CAPÍTULO 1

Comparação entre mulheres hipertensas e normotensas após a menopausa

ESTUDO 1

AMBULATORY BLOOD PRESSURE VARIABILITY AND COMBINED EXERCISE TRAINING: COMPARISON BETWEEN HYPERTENSIVE AND NORMOTENSIVE POSTMENOPAUSAL WOMEN

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ABSTRACT

Aim: The aim of the study was to verify the effects of moderate combined aerobic and resistance exercises training in ambulatory blood pressure (ABPM) and its variability in hypertensive and normotensive postmenopausal women. **Methods:** Twenty-six participants were divided into two groups: hypertensive (HT = 13) and normotensive (NT = 13). They performed 30 sessions of combined exercises (aerobic and resistance exercises at same session) over 10 weeks. We evaluated: resting BP and 24-h ABPM with systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR). To evaluate blood pressure variability (BPV), the following were considered: 24-h SD (SD24), the mean diurnal and nocturnal deviations (SDdn), average real variability (ARV24). **Results:** The two-way analysis of variance showed no difference in ABPM nor BPV responses after training between groups. Both HT and NT groups had similar BP reductions in 24-h DBP ($P < 0.01$; $\Delta NT = -3.1 \pm 1.1$, $\Delta HT = -1.8 \pm 1.2$ mmHg), 24-h area under the curve of DBP ($P = 0.01$; $\Delta NT = -73 \pm 105$, $\Delta HT = -44 \pm 115$ mmHg), and wake DBP ($P < 0.01$; $\Delta NT = -3.4 \pm 1.2$, $\Delta HT = -1.8 \pm 1.3$ mmHg), without differences in BPV responses. Moreover, HT women had higher overall SBP SDdn ($P = 0.01$), SBP ARV ($P = 0.02$), and MBP ARV ($P < 0.01$) than NT women. **Conclusion:** Ten-week combined exercise training resulted in similar BP reductions in hypertensive and normotensive postmenopausal women, but not in BPV responses.

Keywords: ambulatory blood pressure, blood pressure variability, combined exercise, menopause

INTRODUCTION

Aging affects blood pressure (BP) in different ways in men and women. Premenopausal women have lower BP values than men, and after menopause, this situation reverses, with 41% of women becoming hypertensive [1–3]. The incidence increase of hypertension may be related to the nonproduction of estrogen by the ovaries, which causes an increase in sympathetic activity and vasoconstrictive adrenergic responsiveness [4,5].

In addition to its raw values, BP has short-term and long-term fluctuations. These variations can be understood as adaptations of humoral and neural systems to the environment and emotional stimuli, besides helping to diagnose changes in the mechanisms of BP regulation [6]. Thus, through ambulatory blood pressure monitoring (ABPM) it is also possible to evaluate the functioning of the autonomic nervous system by the analysis of blood pressure variability (BPV). High BPV values are related to an increased risk of cardiovascular events and a greater number of target organs lesions [7].

One of the best alternatives for treatment and prevention of hypertension is physical training, because it improves several cardiovascular parameters, such as reductions in SBP and diastolic blood pressure (DBP) values in hypertensive [8] and normotensive individuals [9], after short-term or long-term interventions [10], in addition, to reduce BPV especially in populations with cardiovascular dysfunction [11,12]. However, few studies have compared the BP responses to exercise on ambulatory and BPV measures after combined training (aerobic and resistance exercises at the same session).

Because combined training shows beneficial effects on several health parameters, it is recommended in the guidelines for prevention and treatment of hypertension [13,14]. However, it is worth noting that the magnitude and mechanisms of the exercise hypotensive responses may be different among normotensive and hypertensive individuals [15]. In addition, the effects of physical training on well-controlled hypertensives are still poorly understood, and antihypertensive drugs may influence the ability of the exercise to reduce BP [16]. Thus, the initial hypothesis was that BP reductions after moderate combined exercise training would be more pronounced in hypertensive women. Therefore, the aim of the study is to verify the effects of moderate combined aerobic and resistance exercises training in ambulatory BP and its variability in hypertensive and normotensive postmenopausal women.

MATERIAL AND METHODS:

PARTICIPANTS:

This is a controlled clinical trial study, with BP assessments before and after 10 weeks of combined aerobic and resistance exercises training. Participants were divided into two groups: hypertensive (HT) (n = 13) and normotensive (NT) (n = 13). A total of 260 women, aged 50–70 years, postmenopausal (amenorrhea for at least 12 months) were recruited from traditional media, and 36 nonobese volunteers, who fulfilled the inclusion criteria and agreed to participate in the study. From the initial number of 36 women, 10 women did not complete the entire intervention, so 26 completed 10 weeks of training and perform posttests.

The inclusion criteria for the study were as follows: amenorrhea for at least 12 months; BMI ≤30 kg/m^2; ability to engage in treadmill and resistance exercises; no history of diabetes, cancer or cardiovascular disease (except for hypertension in HT); hypertension nonmedicated with beta-blockers; no hormone therapy or soy-derived supplementation; and nonsmokers. The Human Research Ethics Committee of the Federal University of Uberlândia approved this study (CAAE: 40622414.9.0000.5152). All volunteers signed a Consent Term. The experiments conformed to the principles set out in the World Medical Association Declaration of Helsinki and this research was registered at Clinicaltrials.gov (number: NCT03531034).

EVALUATION OF ANTHROPOMETRY:

In the beginning, we indicated that the volunteers continued their eating habits until the end of the collections, so we performed a food intake analysis through dietary reminders of 24 h, applied by nutritionists on 3 nonconsecutive days. The dietary data analyses were performed using Dietpro (Minas Gerais, MG, Brazil) software (version 5.7i) and the United States Department of Agriculture (USDA) food composition table. This analysis demonstrated that there were no significant changes in macronutrient dietary patterns during 10 weeks of training (data not shown).

The body mass was measured using a Micheletti electronic scale (São Paulo, SP, Brazil), the stature was measured in a Sanny stadiometer (São Paulo, SP, Brazil) and an inelastic tape measuring 0.5 cm wide was used for abdominal circumference measurements. The bioelectrical impedance apparatus of Biodynamics model 450c (Biodynamics, Shoreline, Washington, USA) was used to estimate the total lean body mass, fat mass, and percentage of total body fat mass.

RESTING AND AMBULATORY BLOOD PRESSURES - ABPM

Resting BP and HR was monitored through calibrated and validated automatic oscillometric monitors [17] (Omron® HEM-7113, Shimogyo-ku, Kyoto, Japan) in 3 nonconsecutive days. At pre and post moments, three measurements of systolic BP (SBP), diastolic BP (DBP), and HR were performed and considered as the mean for analysis. Values outside of two standard deviations from individual mean were discarded, being considered the average of the others.

All volunteers were submitted two times to a 24-h BP assessment by ABPM: before and after 10 weeks of combined exercise training, with a minimum of 48 h after the last training session. An ABPM Cardios Dyna- MAPA + device (São Paulo, SP, Brazil) was used associated with a self-report diary of activities of daily living (sleep, work, food, etc.) or any event that could interfere abnormally with BP or device measurements. The device was always placed in the morning (7:00 a.m.) and the measurements were made every 15 min from 7:00 to 23:00 and every 30 min from 23:00 to 7:00. Before use ABPM during daily activities, resting BP was measured using the same equipment after 15 min of rest in sitting position. The monitoring was considered effective when at least 80% of the measures were valid. To analyze the BP curve from 0 to 24 h, it was adopted as time 0 the moment in which the monitor was placed. The following results were evaluated: SBP, DBP, mean blood pressure (MBP) and HR divided into awake, sleep, and 24-h phases.

BLOOD PRESSURE VARIABILITY - BPV

Based on ABPM data, BPV was calculated using three different parameters [18]: 24-h SD weighted by the time interval between consecutive readings (SD24); the mean diurnal and nocturnal deviations weighted for the duration of the daytime and nighttime interval (SDdn); the average real variability (ARV) weighted for the time interval between consecutive readings.

EXERCISE PROGRAM

The exercise program consisted of 30 sessions of combined aerobic and resistance exercises training distributed over 10 consecutive weeks. Each session lasted 45 min and consisted of 5 min warm-up on a treadmill, 20 min of resistance exercise, and 20 min of aerobic exercise. The resistance training was performed using 60% of one maximal repetition test (1RM), that was previously evaluated according to with Kraemer and Fry [19] protocol, in two sets of 15 repetitions in seven exercises of weight training for large muscle groups: Leg press 45º, seated cable row, vertical chest press machine, seated fly machine, wide grip lat pull-down,

squat (with lumbar swiss ball support), and abdominal crunch. The aerobic exercise was performed on treadmill, at a speed of 5.5 km/h and intensity (imposed by treadmill inclination and HR) between ventilatory thresholds 1 and 2 intensities, determined through a test protocol adapted from Puga et al. [20]. After 5 weeks of training, 1RM test was performed again to readjust the resistance training load and aerobic intensity was readjusted by HR predicted in the incremental test.

STATISTICAL ANALYSIS

Sample calculation (n = 24) was performed in G-Power 3.1 software (Effect size f: 0.3; α err: 0.05; power: 0.80). The results are presented as means ± SD. The data distribution was analyzed using the Shapiro–Wilk test and the variances homogeneity was assessed by the Levene test. Variables without normality or homogeneity were transformed into Log and later in Z-score until assuming these assumptions. The two-way analysis of variance for repeated measures was used to analyze the time (pre and post) and group (HT and NT) interactions with a Bonferroni post hoc test, when appropriate. Unpaired Student's t-tests were used to compare variables with only one measurement over time (age, height, and time after menopause) between groups. BP variation over time was analyzed by the area under the curve (AUC) calculated by the trapezoidal method in GraphPad Prism Software version 6. Statistical significance was set as $P < 0.05$. Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for all analyses.

RESULTS

Most hypertensive volunteers used angiotensin-2 AT-1 receptor blocker, associated (30.8%) or not (30.8%) with thiazide diuretics, then we have users of angiotensin-converting enzyme inhibitors, associated (7.7%) or not (15.4%) with thiazide diuretics, and finally, we have users of thiazide diuretics as monotherapy (15.4%).

Among general characteristics, only age presented a statistical difference between groups ($P = 0.003$; HT = 52.7 ± 5.3; NT = 58.9 ± 3.9 years). Other basal characteristics such as time post-menopause ($P = 0.457$; HT = 4.7 ± 3.9; NT = 5.9 ± 3.9 years) and height ($P = 0.622$; HT = 1.57 ± 0.05; NT = 1.58 ± 0.08 m) did not show differences by t-test. The maximum strength evaluation by 1-RM test demonstrated time effects ($P < 0.01$) with no interaction or group effects in the upper (i.e. bench press; ΔHT = 10.00 ± 7.36; ΔNT = 9.69 ± 3.92 kg) and lower limbs (i.e. leg press; ΔHT = 58.08 ± 68.57; ΔNT = 82.85 ± 32.59 kg).

Table 1 shows general characteristic differences between groups and times. These analyses showed interaction effect in body mass (P = 0.04). However, body composition analysis did not show interaction or group effects, but rather effects of time, with reductions of fat mass (P = 0.01) and percentage of fat (P = 0.01), as well as increases in lean mass (P = 0.01) in both groups. Similarly, resting BP and HR analyzes did not show interaction or group effects, but rather effects of time, with reductions of SBP (P = 0.03) and DBP (P = 0.02), without statistical effects in HR.

Table 1 – *General characteristics*

	Pre Mean ± SD	Post Mean ± SD	Δ Mean ± SD	*p* Groups	*p* Time	*p* Inter.
Body Mass (Kg)						
HT	68.51 ± 8.30	67.70 ± 8.14	-0.81 ± 0.68	0.43	0.66	0.04
NT	64.82 ± 8.99	66.06 ± 9.08	1.24 ± 3.43			
BMI (kg/m²)						
HT	27.68 ± 4.57	27.36 ± 4.56	-0.32 ± 0.28	0.72	0.56	0.12
NT	26.89 ± 2.91	27.03 ± 3.40	0.15 ±1.02			
Abdominal circumference (cm)						
HT	93.61 ± 9.21	93.44 ± 8.62	-0.17 ± 2.61	0.64	0.08	0.14
NT	92.92 ± 7.91	91.00 ± 8.06	-1.92 ± 3.17			
Body Fat (%)						
HT	38.42 ± 6.98	37.32 ± 7.34	-1.10 ± 1.61	0.20	0.01	0.71
NT	35.38 ± 3.74	34.52 ± 4.08	-0.86 ± 1.66			
Fat Mass (kg)						
HT	26.50 ± 6.91	25.69 ± 6.95	-0.81 ± 1.17	0.16	0.01	0.51
NT	23.03 ± 4.60	22.53 ± 4.75	-0.51 ± 1.14			
Lean Mass (kg)						
HT	39.20 ± 4.00	39.88 ± 4.22	0.68 ± 1.00	0.15	0.01	0.83
NT	41.60 ± 4.01	42.19 ± 3.90	0.59 ± 1.05			
Systolic Blood Pressure at rest (mmHg)						
HT	121.84 ± 13.68	120.38 ± 6.56	-1.5 ± 12.9	0.52	0.03	0.09
NT	129.08 ± 17.39	119.23 ± 13.13	-9.8 ± 11.3			
Diastolic Blood Pressure at rest (mmHg)						
HT	76.31 ±8.09	75.38 ± 7.71	-0.8 ± 7.1	0.14	0.02	0.07
NT	84.31 ± 12.17	77.77 ± 9.29	-6.5 ± 8.1			
Heart rate at rest (mmHg)						
HT	71.46 ± 9.77	67.61 ± 7.00	-3.9 ± 8.5	0.22	0.51	0.13
NT	73.08 ± 10.94	74.61 ± 11.15	1.5 ± 9.1			

BMI, body mass index; HT, hypertensive group; inter., interaction effect; NT, normotensive group.

Table 2 shows comparisons of ambulatory BP. There are no interaction effects at any analyzed variable. In 24-h parameters, it was possible to observe time effects on DBP ($P < 0.01$) with lower values at post-training in both groups. On sleep parameters, there were group effects on DBP ($P = 0.04$) and MBP ($P = 0.01$), with higher values on HT. Additionally, on wake DBP it was possible to observe time effects ($P < 0.01$) with lower values at post-training in both groups. There was no significant difference among time variations (Δ) in all parameters evaluated.

Table 2 - *Ambulatory blood pressure monitoring*

	Pre Mean ± SD	Post Mean ± SD	Δ Mean ± SD	*p* Groups	*p* Time	*p* Inter.
24h SBP (mmHg)						
HT	122.4 ± 9.8	119.5 ± 7.7	- 2.9 ± 2.2	0.18	0.06	0.98
NT	117.7 ± 10.8	114.9 ± 9.6	- 2.7 ± 1.9			
24h DBP (mmHg)						
HT	75.7 ± 6.2	73.8 ± 6.3	- 1.8 ± 1.3	0.25	< 0.01	0.42
NT	73.5 ± 7.5	70.1 ± 7.1	- 3.4 ± 1.2			
24h MBP (mmHg)						
HT	93.5 ± 5.0	92.7 ± 6.2	- 0.7 ± 1.8	0.05	0.13	0.36
NT	89.8 ± 8.6	86.6 ± 7.3	- 3.2 ± 1.7			
Sleep SBP (mmHg)						
HT	115.8 ± 10.9	112.6 ± 11.5	- 3.5 ± 3.2	0.05	0.41	0.51
NT	106.8 ± 10.7	106.4 ± 11.2	- 0.5 ± 2.8			
Sleep DBP (mmHg)						
HT	69.7 ± 7.4	67.1 ± 7.5	- 2.6 ± 2.3	0.04	0.24	0.56
NT	63.5 ± 7.7	62.6 ± 7.9	- 0.9 ± 1.8			
Sleep MBP (mmHg)						
HT	87.4 ± 6.3	85.9 ± 9.4	-1.5 ± 2.8	0.01	0.51	0.90
NT	79.8 ± 8.2	78.8 ± 8.3	- 0.9 ± 2.4			
Wake SBP (mmHg)						
HT	124.5 ± 10.0	121.6 ± 7.1	- 2.9 ± 2.2	0.40	0.07	0.84
NT	121.2 ± 11.6	118.9 ± 9.0	- 2.2 ± 1.7			
Wake DBP (mmHg)						
HT	77.6 ± 6.2	75.8 ± 6.7	- 1.8 ± 1.2	0.46	< 0.01	0.44
NT	76.3 ± 8.1	73.1 ± 7.0	- 3.1 ± 1.1			
Wake MBP (mmHg)						
HT	95.5 ± 5.0	94.8 ± 5.7	- 0.7 ± 1.7	0.18	0.13	0.35
NT	93.1 ± 9.3	90.2 ± 7.2	- 2.8 ± 1.5			

DBP, diastolic blood pressure; HT, hypertensive group; inter., interaction effect; MBP, mean blood pressure; NT, normotensive group; SBP, systolic blood pressure.

Table 3 shows BPV data. There are no interactions or time effects at any variable. It was possible to observe group effects on SBP SDdn (P = 0.01), ARV SBP (P = 0.02), and ARV MBP (P < 0.01) with higher values on HT.

Table 3 - *Blood pressure variability*

	Pre Mean ± SD	Post Mean ± SD	Δ Mean ± SD	*p* Groups	*p* Time	*p* Inter.
SD_{24} SBP (mmHg)						
HT	12.7 ± 2.1	13.0 ± 2.0	0.3 ± 0.5	0.35	0.78	0.48
NT	12.3 ± 4.3	11.7 ± 2.7	- 0.7 ± 1.2			
SD_{24} DBP (mmHg)						
HT	9.4 ± 1.5	10.1 ± 1.3	0.6 ± 0.5	0.30	0.27	0.37
NT	9.7 ± 2.1	9.9 ± 2.2	0.2 ± 0.8			
SD_{24} MBP (mmHg)						
HT	9.8 ± 2.0	10.0 ± 1.6	0.2 ± 0.6	0.75	0.99	0.77
NT	9.8 ± 2.9	9.6 ± 2.3	- 0.2 ± 1.0			
SDdn SBP (mmHg)						
HT	11.6 ± 1.0	12.2 ± 2.1	0.5 ± 0.4	0.01	0.78	0.37
NT	10.3 ± 2.6	10.0 ± 2.0	- 0.3 ± 0.8			
SDdn DBP (mmHg)						
HT	8.5 ± 1.4	9.0 ± 1.3	0.4 ± 0.4	0.17	0.10	0.59
NT	7.7 ± 1.3	8.6 ± 2.0	0.9 ± 0.7			
SDdn MBP (mmHg)						
HT	8.8 ± 1.6	9.0 ± 1.3	0.1 ± 0.4	0.07	0.56	0.73
NT	7.7 ± 1.6	8.1 ± 1.9	0.4 ± 0.7			
ARV SBP (mmHg)						
HT	10.7 ± 1.2	10.2 ± 1.9	- 0.5 ± 0.3	0.02	0.52	0.46
NT	9.1 ± 1.2	9.1 ± 2.3	0.03 ± 0.7			
ARV DBP (mmHg)						
HT	7.7 ± 1.3	8.0 ± 1.5	0.3 ± 0.4	0.05	0.28	0.98
NT	6.6 ± 1.3	7.0 ± 1.2	0.3 ± 0.4			
ARV MBP (mmHg)						
HT	7.7 ± 1.2	7.5 ± 1.3	- 0.2 ± 0.4	< 0.01	0.91	0.45
NT	6.4 ± 1.0	6.6 ± 1.1	0.2 ± 0.4			

ARV, the average real variability weighted for the time interval between consecutive readings; DBP, diastolic blood pressure; HT, hypertensive group; inter., interaction effect; MBP, mean blood pressure; NT, normotensive group; SBP, systolic blood pressure. SD24, 24-h SD weighted by the time interval between consecutive readings; SDdn, the mean diurnal and nocturnal deviations weighted for the duration of the daytime and nighttime interval.

In *Figure 1*, panels A and B present 24-h values used to AUC calculation of SBP and DBP, respectively; panels C and D present the values of AUC of SBP and DBP, respectively. No significant Interaction or group effects were found in any of the investigated parameters. On the other hand, it was possible to observe time effects on DBP (P = 0.012) with lower values at post-training in both groups.

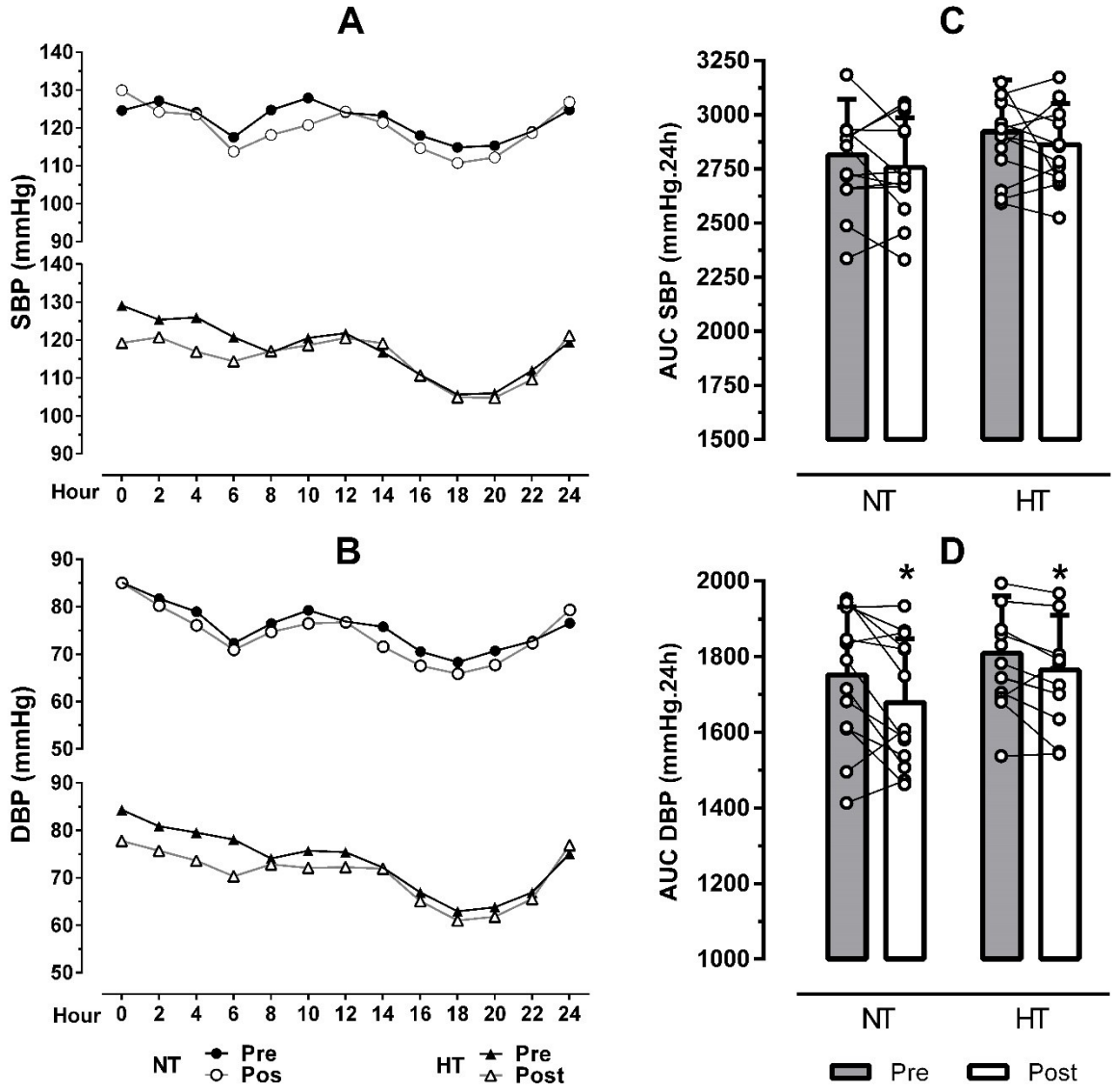

Figure 1 – *Twenty-four-hour blood pressure (BP) and the correspondent area under the curve. (panels a and b) Mean values of systolic and diastolic BP, respectively. (panels c and d) Values of 24-h area under the curve of systolic and diastolic BP, respectively, in these panels the circles connected by lines represent individual values. AUC, area under the curve; DBP, diastolic blood pressure; HT, hypertensive group; NT, normotensive group; SBP, systolic blood pressure; *: time effect (P < 0.05).*

DISCUSSION

The present study demonstrates that 10 weeks of combined moderate-intensity exercise were able to improve BP in both groups, without a significant difference between them. After 10 weeks, there was a reduction (time effects) in 24-h DBP, Wake DBP, AUC SBP, and AUC DBP, but there was no change in BPV parameters in both groups. In addition, there were group effects, with higher HT values in ABPM (sleep SBP, DBP, and MBP) and its variability (24-h MBP, SDdn SBP, ARV SBP, ARV DBP, and ARV MBP).

Another important result of the present study was that the effects of the training were better evidenced in awake compared to sleep phase. Similar result was found in the short-term[21], in which on the day of the exercise there was no reduction during night. According to a meta-analysis, this kind of response was verified in normotensive and hypertensive adults [8]. Possibly, these response pattern is related to reduction of sympathetic activity [22], which during the sleep period is naturally reduced.

Behavioral changes are recommended for control and prevention of arterial hypertension, among them: weight reduction, control of sodium and alcohol consumption, and regular physical exercise. These changes appear to have distinct quantitative and qualitative effects on BP but potentialized when performed together [23]. Among these strategies, we highlight moderate combined training, that is recommended as a nonpharmacological strategy in various guidelines [13,14,24], that show hypotensive responses mainly in DBP [8], but promising results also in SBP [16]. On the other hand, it is important to highlight that are recommendations for exercise doses, because the hypotensive responses are dependents of the intensity, volume, and duration of the exercise, in addition to baseline BP values [8]. In this sense, exercise with moderate intensity for hypertensive patients after menopause has positive aspects related to exercise tolerance and adherence to training [22], also being sufficient to provide significant changes in BP [25,26] and BPV [27] after its performance.

It is known that physical training improves aerobic fitness and physiological adaptations to cardiovascular health in hypertensive and normotensive patients, including postmenopausal women [9], and is able to reduce the risk of cardiovascular diseases from 30 to 40% in all populations [22]. Although no significant difference between groups was demonstrated, the effect of combined training was beneficial for both, since reductions around 5 mmHg of SBP and 2 mmHg of DBP are sufficient to reduce the risk of stroke in 13 and 11.5%, respectively [28], similar values to those found in the present study especially in ambulatorial DBP. Comparable results with normotensive women were found in other studies, such as those performed by Mandrup et al. [29], in which 3 months of training demonstrated DBP reduction and other health parameters improvements in postmenopausal women, being a group predisposed to develop cardiovascular diseases, the exercise acts as a prevention of hypertension and other health risk factors [22].

Previous studies [30] have also found significant hypotensive responses after conducting combined training in hypertensive postmenopausal women, but with greater magnitude, which may be related to the higher baseline values (SBP = 152 mmHg, DBP = 95

mmHg) in comparison with those of the present study (SBP = 122 mmHg, DBP = 76 mmHg). Although hypertensive, and with values significantly higher than the NT group, baseline 24-h BP values were still close to the recommended values, which may influence the magnitude of the hypotensive response after training in the present study.

Concerning the possible physiological mechanisms responsible for these BP falls, a recent review [22] describe various of these mechanisms, which can have central action as increased baroreflex sensitivity and reduction of autonomic dysfunction, with increase vagal tonus and reduction of sympathetic tone; or peripherical action as improvements of endothelial function induced by serum increase of vasodilators such as acetylcholine and bradykinin, improvements in nitric oxide metabolism due to increased enzymatic activity and phosphorylation of nitric oxide synthase enzyme, as well as increases in nitrite/nitrate and nitrogen oxide serum concentrations that cause endothelium-dependent vasodilation, reduced vascular resistance and improved arterial stiffness in peripheral arteries.

In addition to reduce BP, these variations in vascular activity are closely related to improvements in BPV caused by exercise [27] and antihypertensive drugs [31]. It is worth noting that there are pieces of evidence that the magnitude of BPV is independent of BP absolute levels and correlates closely with target organ damage and with the incidence of cardiovascular events [11]. Therefore, physical exercise in postmenopausal women attenuates arterial aging, promoting important functional vascular adaptations, such as reduction of arterial stiffness [22] in this population. In addition, the structural adaptations that allow distension of the arterial wall obtained with physical exercise are fairly stable, which makes it possible to maintain BP values close to the recommended [3,32].

A possible mechanism that may explain the absence of improvement after training is the loss of estrogen after menopause, which appears to be linked to a decrease in β-adrenergic vasodilation and an increased risk of hypertension in older women [4], attenuating responses in both groups. Other important factors that contribute to mitigating BPV differences between groups are obesity and arterial stiffening associated with aging [33]. Specifically for HT, the use of antihypertensive drugs capable to improve BPV, like angiotensin receptor blockers [34] (those predominant in the present study), may have saturated the mechanism of action of exercise training given the endothelium-dependent mechanism of both [27,31], preventing more pronounced responses in this group. On the other hand, the group effects found on ambulatory BP and BPV corroborate with that found in the literature [35], in which hypertensive women, have higher baseline BP and BPV than normotensive women. So, these

differences can be explained by the worse vascular and autonomic health associated with hypertension [22].

In view of what has been shown, we note that this study has limitations that should be highlighted. First, it is a small sample (n = 26), which in view of the high prevalence of hypertension worldwide may have difficulties in generalizing under different circumstances. However, it is worth note that the final sample is in accordance with the initial sample calculation. Furthermore, we did not standardize antihypertensive drugs and their doses, but the volunteers had to stay with the same drug and dose throughout the study. Although there was a significant difference in age between HT and NT groups, and this difference could influence BP responses due to vascular aging, we highlight that women in both groups were middle-aged (age between 50 and 60 years), and they were with similar time after menopause, probably in the same climacteric phase. Finally, the lack of groups without physical training can limit the comprehension of the effects of exercise. However, BP reductions after physical exercise training have already been demonstrated in the literature extensively [15,16,26,36] with different populations (men, women, youth, elderly, healthy, or sick) and exercise characteristics (aerobic, resistance, isometric, combined, etc.) which we believe that minimizes the idiosyncratic problems of our experimental design. Thus, these results cannot be generalized to men, women in different stages of life and climacteric, users of antihypertensive drugs different from those presented or with different characteristics of physical training.

CONCLUSION

Ten weeks of moderate combined aerobic and resistance exercise training resulted in similar reductions in ambulatory BP in both hypertensive and normotensive postmenopausal women, although it results in no effect on BP variability.

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Conflicts of Interest: The authors declare no conflict of interest.

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TREND statement checklist
(Transparent Reporting of Evaluations with Non-randomized Designs)

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg
TITLE AND ABSTRACT				
Title and Abstract	1	Information on how unit were allocated to interventions	✓	17
		Structured abstract recommended	✓	17
		Information on target population or study sample	✓	17
INTRODUCTION				
Background	2	Scientific background and explanation of rationale	✓	18
		Theories used in designing behavioral interventions	✓	18
METHODS				
Participants	3	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	✓	19
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	✓	19
		Recruitment setting	✓	19
		Settings and locations where the data were collected	✓	19
Interventions	4	Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	✓	19-21
		• *Content: what was given?*	✓	20-21
		• *Delivery method: how was the content given?*	✓	20-21
		• *Unit of delivery: how were the subjects grouped during delivery?*	×	-
		• *Deliverer: who delivered the intervention?*	×	-
		• *Setting: where was the intervention delivered?*	✓	19
		• *Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?*	✓	20
		• *Time span: how long was it intended to take to deliver the intervention to each unit?*	✓	20
		• *Activities to increase compliance or adherence (e.g., incentives)*	×	-
Objectives	5	Specific objectives and hypotheses	✓	18
Outcomes	6	Clearly defined primary and secondary outcome measures	×	-
		Methods used to collect data and any methods used to enhance the quality of measurements	✓	19-21
		Information on validated instruments such as psychometric and biometric properties	✓	19-20
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	✓	21
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	✓	19
		Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	✓	19
		Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	×	-
Blinding (masking)	9	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	×	-
Unit of Analysis	10	Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	✓	19
		If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	×	-
Statistical Methods	11	Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	✓	21
		Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	×	-

		Methods for imputing missing data, if used	×	-
		Statistical software or programs used	✓	21
RESULTS				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	✓	19
		• *Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study*	✓	19
		• *Assignment: the numbers of participants assigned to a study condition*	✓	19
		• *Allocation and intervention exposure: the number of participants assigned to each condition and the number of participants*	✓	19
		• *Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition*	✓	19
		• *Analysis: the number of participants included in or excluded from the main analysis, by study condition*	✓	19
		Description of protocol deviations from study as planned, along with reasons	×	-
Recruitment	13	Dates defining the periods of recruitment and follow-up	✓	19
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	✓	21-22
		Baseline characteristics for each study condition relevant to specific disease prevention research	✓	2-22
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	×	-
		Comparison between study population at baseline and target population of interest	✓	21-22
Baseline equivalence	15	Data on study group equivalence at baseline and statistical methods used to control for baseline differences	✓	21-22
Numbers analyzed	16	Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	19
		Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	×	-
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	×	-
		Inclusion of null and negative findings	✓	22-25
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	×	-
Ancillary analyses	18	Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	×	-
Adverse events	19	Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	×	-
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	25-28
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	27
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	✓	28
		Discussion of research, programmatic, or policy implications	✓	28
Generalizability	21	Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study.	✓	28
Overall Evidence	22	General interpretation of the results in the context of current evidence and current theory	✓	28

ESTUDO 2

EFFECT OF COMBINED EXERCISE ON HEART RATE VARIABILITY IN NORMOTENSIVE AND HYPERTENSIVE POSTMENOPAUSAL WOMEN

Igor M. Mariano, Victor H. de Freitas, Jaqueline P. Batista, Tállita C. F. Souza, Ana Luiza Amaral, Juliene G.C. Dechichi, Mateus L. Rodrigues, Victor H. V. Carrijo, Guilherme M. Puga.

Status: publicado. Formato original disponível no Anexo 2.

MARIANO, I. M.; FREITAS, V. H. De; BATISTA, J. P.; SOUZA, T. C. F. De; AMARAL, A. L.; DECHICHI, J. G. C.; RODRIGUES, M. L.; CARRIJO, V. H. V.; PUGA, G. M. Effect of combined exercise training on heart rate variability in normotensive and hypertensive postmenopausal women. **Motriz**, [s. l.], v. 27, 2021.

ABSTRACT

AIMS: The aim of this study was to verify and compare the effects of 10 weeks of combined exercise training on the heart rate variability of normotensive (NT) and hypertensive (HT) postmenopausal women. **METHODS:** This is a quasi-experimental controlled clinical trial. Therefore, 14 HT and 12 NT postmenopausal women completed 10 weeks of combined exercise training. The exercise protocol consisted of 45 min of exercise, performed 3 times a week, consisting of 5 min of warm-up, 20 min of resistance exercise, and 20 min of aerobic exercise. Heart rate variability assessments were performed before and after the end of physical training. **RESULTS**: Heart rate variability was assessed pre- and post-training period. Mean RR (ΔNT = 95 ± 88; ΔHT = 38 ± 127), SDNN (ΔNT = 9 ± 13; ΔHT = 3 ± 14), RMSSD (ΔNT = 10 ± 12; ΔHT = 2 ± 18), SD1 (ΔNT = 7 ± 8; ΔHT = 1 ± 13), and SD2 (ΔNT = 10 ± 18; ΔHT = 4 ± 17) showed improvements after the intervention (time effects $p < 0.05$). No parameters presented group or interaction effects ($p \geq 0.05$). **CONCLUSION:** Combined exercise training may be used to improve autonomic modulation of the heart rate of postmenopausal women, regardless of the presence of hypertension.

Key Words: Autonomic Nervous System; Aerobic Exercise; Resistance Exercise; Blood Pressure.

INTRODUCTION

Heart rate variability (HRV) is a non-invasive measurement to evaluate the autonomic modulation of heart rate (HR) [1,2]. Decreased HRV is related to an increased risk of arrhythmia and sudden cardiac death [1]. Although HRV decreases with aging [3], this effect is pronounced after menopause [4,5], when the decreased level of estrogen may interfere with the modulation of cardiovascular autonomic control [6]. Therefore, it is relevant to investigate strategies capable of improving HRV in these women.

The benefits of physical exercise training to improve HRV have been previously reported in meta-analyses [7–10]. In postmenopausal women, the positive effect of isolated aerobic exercises [11] and combined with resistance exercises training (i.e. combined exercise training; CET) [12] to improve HRV have already been reported. In addition to the benefits of CET with regard to cardiac autonomic control, this kind of exercise is recommended by the American College of Sports Medicine to maintain and improve cardiovascular and muscular health and functioning of healthy and old adults [13,14]. Furthermore, CET may positively influence systemic inflammation and oxidative stress, bone health, and climacteric symptoms related to being postmenopausal [15,16]. These factors encourage postmenopausal women to include CET as a training strategy in their lives.

In postmenopausal women, the incidence of hypertension is higher compared to men of a similar age and women before menopause [17]. It is part of the risk groups of cardiovascular diseases, which are the main causes of mortality in the world [18]. Previous studies have shown that hypertensive (HT) patients presented worse HRV indices compared to normotensive (NT) subjects, indicating poor cardiac autonomic control [12,19]. The CET, in turn, may improve HRV parameters in HT premenopausal women [20]. However, in HT postmenopausal women, the effect of CET on HRV has not yet been shown. Furthermore, although CET may have a positive effect on the HRV of NT postmenopausal women [12], studies are necessary to identify if similar benefits could be reported in HT postmenopausal women.

So, the aims of this study were to verify the effects of 10 weeks of CET on the HRV of NT and HT postmenopausal women and compare the responses between these groups. The hypothesis is that CET would improve HRV parameters in both HT and NT postmenopausal women, with higher improvements in HT subjects. This hypothesis was raised since HT subjects could have had a reduced HRV compared to NT subjects [21,22], presenting more amenability to the training.

METHODS

EXPERIMENTAL APPROACH TO THE PROBLEM

This is a quasi-experimental controlled clinical trial study, in which HRV was monitored in the HT and NT groups before and after 10 weeks of CET. An incremental treadmill test was performed a minimum of 72 h before the first day of training to identify the intensity of aerobic training. Body mass, height, and body mass index were measured before treadmill testing. Pre-, post-5 weeks, and post-10 weeks of training, participants performed the one maximum repetition test (1RM) to identify the resistance training workload. All tests were performed respecting 48 h without exercise and a minimum of 48 h between tests. HRV recording was performed before and after 10 weeks of training, respecting 48 h without exercise. The study design is presented in *Figure 1*. Privation of caffeine and alcohol for 24h was required for all tests.

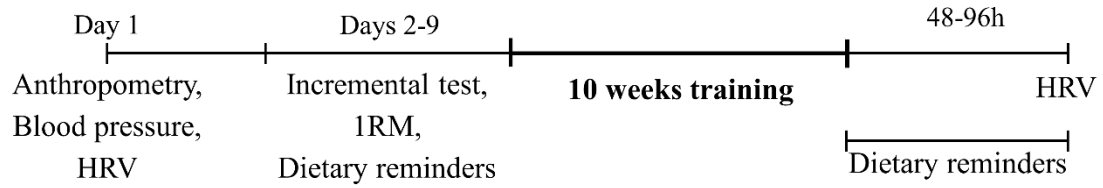

Figure 1 – *Study design. HRV: Heart rate Variability; 1RM: one maximum repetition test.*

SUBJECTS

A total of 383 postmenopausal women, aged 50–70 years, recruited from traditional media (TV, radio and posters) in 2015 and 2016 agreed to participate, of which 40 fulfilled the inclusion criteria. The entire study was carried out at the Federal University of Uberlândia. So, 26 subjects (14 hypertensive [HT] and 12 normotensives [NT]) completed the training (*Figure 2*). The inclusion criteria were amenorrhea for at least 12 months; body mass index ≤ 30 kg/m^2; ability to engage in treadmill and resistance exercises; no history of diabetes, cancer or cardiovascular disease (except for hypertension); not using beta-blockers; no hormone therapy; and non-smokers. This study was approved by the local ethics committee (CAAE: 40622414.9.0000.5152), and all volunteers were informed of the benefits and risks of the investigation prior to signing informed consent agreeing to participate. This research has been conducted in accordance with the principles set forth in the Helsinki Declaration and was

registered at Clinicaltrials.gov (number: NCT03531034). The present study presents secondary data from this registry of which the primary data have already been published[23].

The short form of International Physical Activity Questionnaire (IPAQ) was used to evaluate the initial level of physical activity of the volunteers. All participants were instructed to maintain their regular eating habits throughout the study. Furthermore, a food intake analysis through 24-h dietary reminders was applied by nutritionists on three non-consecutive days before and after training. The dietary data analyses were performed using a web-based program (DIETPRO® 5.7i; Minas Gerais, MG, Brazil) and the United States Department of Agriculture food composition table. This analysis demonstrated that there were no significant changes in dietary patterns during the training (data not shown).

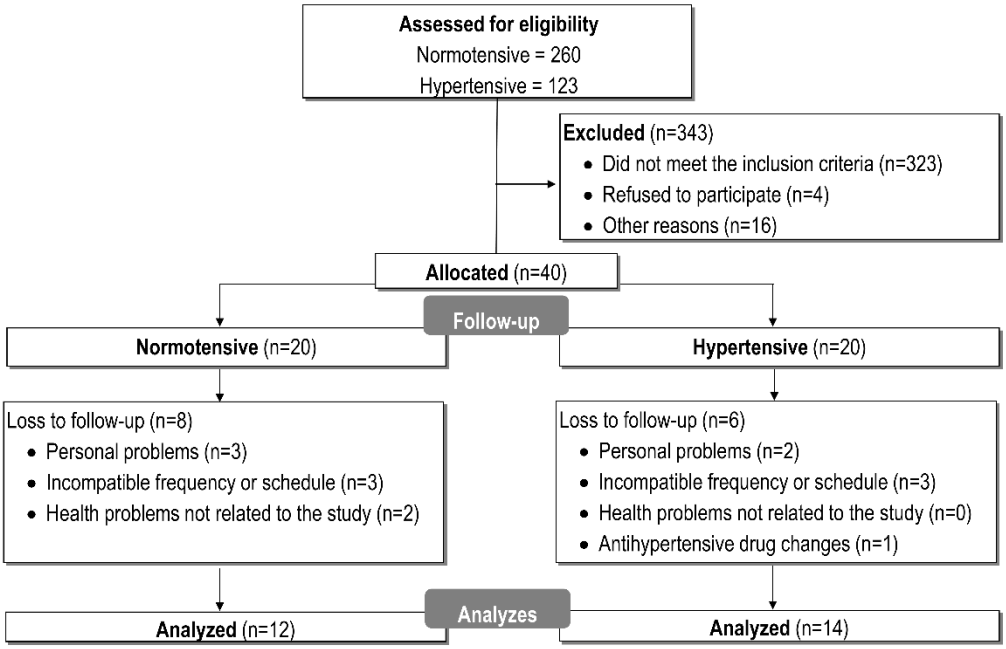

Figure 2 – *Follow-up flowchart*

PROCEDURES

Resting blood pressure was monitored through calibrated and validated automatic monitors [24] (OMRON® HEM-7113, Shimogyo-ku, Kyoto, Japan) on three non-consecutive days. At each moment, three measurements of systolic BP (SBP) and diastolic BP (DBP) were performed, and the mean was considered for analysis.

The incremental treadmill test was adapted from Puga et al. [25]. Briefly, all volunteers performed a submaximal incremental test on a treadmill at 5.5 km/h, and the intensity was increased using treadmill inclination (1% every 2 min) until volunteers reached 85% of their predicted maximum HR or 18 of perceived exertion using the Borg Scale. Oxygen uptake and

carbon dioxide output were recorded during all tests using a gas analyzer (COSMED QUARK CPET gas analyzer, Rome, Italy). The goal of this test was to identify ventilatory thresholds based on ventilatory equivalents.

The intensity of resistance exercise was evaluated and prescribed based on the 1RM. This test consisted of a warm-up of two sets of the exercise to be performed at intensities around 50% and 80% of the subjective estimate of 1RM, with eight and three repetitions, respectively. After this, a maximum of five attempts per exercise was allowed to find the highest workload at which the volunteer could only make one full movement with a 3-min rest between attempts [26].

Resting R-R intervals were recorded for 20 min in the seated position using a HR monitor (POLAR® RS800cx; Polar Electro Oy, Finland; sampling frequency = 1000 Hz) with spontaneous breathing. Data were downloaded to a computer using an infrared interface with specific software (POLAR PRO TRAINER5®, Polar Electro, Kempele, Finland). HRV analysis was performed using KUBIOS HRV 3.0 (University of Kuopio, Kuopio, Finland) [27]. Prior to the analysis, the signal was visually inspected and filtered, and a range of 5 min with few artifacts was selected close to the end of the recording for analysis.

The resulting R-R intervals were analyzed in the time domain, in the frequency domain using spectral analysis (Fast Fourier Transform), and nonlinearly through the Poincaré plot [27]. The time domain indices analyzed included the square root of the mean squared difference of successive R-R intervals (RMSSD), the standard deviation of all normal R-R intervals recorded at an interval of time (SDNN), and the percentage of pairs of adjacent RRi differing by more than 50 ms in the whole recording (pNN50). In the frequency domain, the data series were interpolated at 4 Hz, after which removal of the signal linear trend component was performed using the smooth prior approach.

In the frequency domain, oscillations of R-R intervals were examined within the low-frequency (LF: 0.04–0.15 Hz) and high-frequency bands (HF: 0.15–0.40 Hz). LF and HF were expressed in normalized units. The sympathovagal balance was obtained through the ratio of the LF to HF (LF/HF) bands [1]. For nonlinear indices, the Poincaré plot was examined, and the transversal (SD1) and longitudinal (SD2) axes of the ellipse-like dispersion were calculated.

The exercise program consisted of 30 sessions of combined exercise training performed over 10 consecutive weeks. Each session lasted 45 min and consisted of 5 min of warm-up on

a treadmill (5.5 km/h and 0% inclination), 20 min of resistance exercise, and 20 min of aerobic exercise. The resistance training was performed in two sets of 15 repetitions at 40% of 1RM with 1 min intervals in seven exercises for large muscle groups: leg press 45º, seated low row, vertical chest press, pec deck, wide grip lat pull-down, Swiss ball squat, and abdominal crunch. The aerobic exercise was performed on a treadmill at a velocity of 5.5 km/h with an intensity (imposed by the treadmill inclination test reported above) between ventilatory thresholds 1 and 2. After 5 weeks of training, the intensity of the resistance training was adjusted based on a new 1RM, and the intensity of the aerobic exercise was readjusted through a 20% increase in treadmill inclination.

STATISTICAL ANALYSIS

The sample calculation (minimum n = 24) was performed in G-Power 3.1 (Universität Düsseldorf, Germany) software (α err = 0.05 and power = 0.80), considering RMSSD as the mean variable and 10.3 ± 17.0 ms as possible variations in this index after a medium intensity training phase in postmenopausal women [20]. A Cohen's d of 0.6058 was found, which was then transformed into effect size f for the sample calculation (0.3029). Characteristics and anthropometric values were compared by the t test for independent samples. Frequencies of physical activity levels were compared using the Chi-square test with the exact Monte Carlo test when the expected count was less than 5. Normality of data was tested using the Shapiro-Wilk test. A two-factor (time and group) generalized estimating equation technique (GEE) was performed for between, within, and interaction comparisons. Mean RR, LF, HF and SD2/SD1 presented normality and were analyzed using a linear model. Since some data of pNN50 presented values of 0, this variable was analyzed using a linear model. Other variables were analyzed using the gamma with log link model. All analyses were performed using IBM® SPSS® Statistics 20. The significance level adopted was $p < 0.05$.

RESULTS

Table 1 shows the anthropometric, activity level, and drug characteristics of the volunteers. There was a difference only in age, which was higher in the HT group compared with the NT group. HRV parameters (mean and standard deviation) are described in *Table 2*. Mean RR ($p < 0.01$), SDNN ($p = 0.03$), RMSSD ($p = 0.03$), SD1 ($p = 0.03$), and SD2 ($p = 0.04$) showed time effects (table 2). No parameters had group ($p > 0.05$) or interaction ($p > 0.05$) effects.

Table 1 – *General characteristics in Mean ± Standard Deviation or frequency (% within group).*

	NT (n=12)	HT (n=14)	
Characteristics			**p (t test)**
Age (years)	53.1 ± 5.3	58.7 ± 3.8	<0.01
Amenorrhea (years)	5.0 ± 3.9	7.2 ± 6.2	0.30
SBP (mmHg)	128 ± 18	122 ± 13	0.30
DBP (mmHg)	84 ± 13	76 ± 8	0.06
Height (m)	1.57 ± 0.06	1.58 ± 0.07	0.60
Body Mass (kg)	64.9 ± 9.4	69.2 ± 8.4	0.22
BMI (kg/m²)	26.9 ± 3.0	27.9 ± 4.5	0.53
Physical Activity level			**p (X^2)**
Sedentary (n)	-	-	0.33
Irregularly active (n)	7 (58.3)	6 (42.9)	
Active (n)	4 (33.3)	8 (57.1)	
Very active (n)	1 (8.3)	-	
Antihypertensives			
ACEi (n)	-	1 (7.1)	-
ACEi + Diuretic (n)	-	1 (7.1)	-
ARB (n)	-	4 (28.6)	-
ARB + Diuretic (n)	-	5 (35.7)	-
Thiazide Diuretic (n)	-	3 (21.4)	-
Other medicines			
Calcium (n)	1 (8.3)	3 (21.4)	-
Statin (n)	2 (16.6)	3 (21.4)	-
Anti-depressant (n)	-	2 (14.3)	-
PPI (n)	-	1 (7.1)	-
Beclomethasone (n)	-	1 (7.1)	-
Levothyroxine (n)	1 (8.3)	-	-

NT: Normotensive group; HT: Hypertensive group; SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ACEi: Angiotensin converting enzyme inhibitor; ARB: Angiotensin 1 receiver blockers; PPI: Proton pump inhibitor.

Table 2 - *Heart rate variability.*

	Groups	Pre (mean ± SD)	Post (mean ± SD)	p Group	p Time	p Interaction	Achieved Power*
Mean RR	NT HT	760 ± 105 813 ± 132	855 ± 114 851 ± 87	0.50	<0.01	0.16	0.75
SDNN	NT HT	20.9 ± 14.3 21.8 ± 12.2	29.7 ± 17.2 24.7 ± 9.0	0.69	0.03	0.31	0.56
RMSSD	NT HT	15.6 ± 11.4 21.4 ± 16.0	25.9 ± 14.9 23.4 ± 9.6	0.60	0.03	0.12	0.77
pNN50	NT HT	2.4 ± 6.7 7.9 ± 13.2	8.0 ± 10.5 5.3 ± 6.8	0.64	0.48	0.05	0.95
LF	NT HT	73.7 ± 9.5 65.0 ± 21.8	67.6 ± 18.2 67.1 ± 13.8	0.29	0.66	0.36	0.42
HF	NT HT	26.3 ± 9.5 34.9 ± 21.8	32.3 ± 18.1 32.8 ± 13.8	0.29	0.66	0.36	0.41
SD1	NT HT	11.1 ± 8.1 15.1 ± 11.3	18.3 ± 10.5 16.5 ± 6.8	0.60	0.03	0.12	0.77
SD2	NT HT	27.4 ± 18.7 26.4 ± 13.7	37.3 ± 22.7 30.5 ± 11.3	0.52	0.04	0.46	0.39
SD2/SD1	NT HT	2.63 ± 0.63 2.18 ± 0.85	2.22 ± 0.78 1.98 ± 0.56	0.07	0.11	0.59	0.17

*NT: Normotensive group; HT: Hypertensive group; SDNN: Standard deviation of normal RR intervals; RMSSD: Root Mean Square of the Successive Differences of RR intervals; pNN50: percentage of pairs of adjacent RR intervals differing by more than 50 milliseconds; LF: Low frequency; HF: High frequency; SD1: Standard deviations of the distances from points to diagonal Y = X of the scattergram.; SD2: Standard deviations of the distances from points to straight "Y = -X+RR_{mean}" of the scattergram; * Achieved power analysis was based on interaction effect sizes.*

DISCUSSION

The hypothesis of the present study was that CET could promote greater improvement in HRV in HT postmenopausal women compared to NT postmenopausal women. Our results refute this hypothesis, since we found no differences between NT and HT postmenopausal women in adaptations to CET in mean RR, SDNN, RMSSD, SD1 and SD2.

A greater effect of CET on the HRV of HT postmenopausal women was expected, because the cardiac autonomic modulation of HT subjects at rest was impaired, reflecting in lower general and vagal parameters of HRV [21,22]. For example, the overall variability measured by SDNN can be up to 15% lower in HT when compared to healthy ones [21]. Apparently, a trainability effect was expected on HRV, with subjects with lower HRV having a higher effect with training [28]. This improvement can reach up to 50% of the overall

variability measured by SDNN after combined training in women [20]. However, participants of the present study presented well-controlled hypertension (SBP: 121.8 ± 13.1 mm Hg; DBP: 76.0 ± 7.8 mm Hg), which may have mitigated the autonomic differences between the HT and NT groups (Table 2). So, the use of antihypertensive drugs may explain why we did not find statistical differences between the groups. However, only the use of atenolol, with or without amlodipine, is related to modifications in HRV at rest in HT patients [29], which is a family of medicines not used by subjects in the present study. Therefore, additional studies are desired to investigate if antihypertensive drugs may affect rest HRV as well as the effect of exercise training on the HRV of HT postmenopausal women. Up to now, the results suggest no differences between well-controlled HT and NT postmenopausal women in HRV.

The time effects in the majority of HRV parameters suggest that CET improved the cardiac autonomic control of both NT and HT postmenopausal women. Among these parameters, the RMSSD, pNN50 and SD1 are most affected by high-frequency variations in the HR and are frequently used as a marker of good cardiac vagal modulation [1]. Therefore, the improvement of these parameters suggest that CET increased the resting cardiac vagal modulation of postmenopausal women. These improvements are common physiological adaptations promoted by aerobic training, and an increase in parasympathetic parameters is frequently reported after a phase of training [30]. Improvements in RMSSD and SD1 as a result of CET were previously reported in NT postmenopausal women [12], corroborating with the results found. However, in accordance with our searches, the improvement in cardiac vagal modulation parameters with CET in HT postmenopausal women is shown for the first time and should be highlighted.

Time effects were reported for mean RR, SDNN and SD2 too. These parameters are influenced by both low- and high-frequency variations of the HR, therefore, being associated as global parameters of cardiac autonomic control [1]. The positive effect of CET on the mean RR in NT postmenopausal women was shown previously [12]. These results suggest that, in addition to improvement on cardiac vagal modulation, CET may promote an improvement in the global cardiac autonomic modulation of postmenopausal women. In this population, improvements in autonomic control of the HR are relevant due to the increased risk of cardiovascular diseases associated with low autonomic control of the cardiovascular system [3–5,31]. Studies investigating the effects of CET on HRV in HT postmenopausal women are scarce, making it difficult to compare the results reported here. However, in HT middle-aged sedentary women, CET improved HRV [20]. In these women, the increase in global HRV is an

important clinical effect due the decreased cardiac autonomic modulation reported in this population [2,19], with up to 30% decrease in overall variability as measured by SDNN[4].

It is worth mentioning that these results reported on the present study refer to medicated HT postmenopausal women and to an intervention with combined exercise training with moderate intensity. Therefore, they cannot be generalized to women with untreated or uncontrolled hypertension, men, or exercises with other characteristics. Future study with a similar design and the presence of a group without antihypertensive drugs could help us to explain the results found. As possible limitations, we report that there is no group without exercise as an intervention and no control of antihypertensive drug classes and doses. Finally, we reiterate the importance of physical exercises after menopause regardless of the existence of hypertension, since besides autonomic control alterations, they can generate improvements in: blood pressure [23,32,33], lipid profile [15], endothelial function [34], oxidative profile [35], climacteric simptoms [36] and general cardiovascular health [33,37].

CONCLUSION

In summary, 10 weeks of CET improved the HRV parameters of both NT and HT postmenopausal women without significant differences.

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TREND statement checklist
(Transparent Reporting of Evaluations with Non-randomized Designs)

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg
TITLE AND ABSTRACT				
Title and Abstract	1	Information on how unit were allocated to interventions	✓	36
		Structured abstract recommended	✓	36
		Information on target population or study sample	✓	36
INTRODUCTION				
Background	2	Scientific background and explanation of rationale	✓	37
		Theories used in designing behavioral interventions	✓	37
METHODS				
Participants	3	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	✓	38
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	✓	38
		Recruitment setting	✓	38
		Settings and locations where the data were collected	✓	38
Interventions	4	Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	✓	39-41
		• *Content: what was given?*	✓	39-41
		• *Delivery method: how was the content given?*	✓	39-41
		• *Unit of delivery: how were the subjects grouped during delivery?*	×	-
		• *Deliverer: who delivered the intervention?*	×	-
		• *Setting: where was the intervention delivered?*	✓	38
		• *Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?*	✓	40
		• *Time span: how long was it intended to take to deliver the intervention to each unit?*	✓	40
		• *Activities to increase compliance or adherence (e.g., incentives)*	×	-
Objectives	5	Specific objectives and hypotheses	✓	37
Outcomes	6	Clearly defined primary and secondary outcome measures	×	-
		Methods used to collect data and any methods used to enhance the quality of measurements	✓	39-41
		Information on validated instruments such as psychometric and biometric properties	✓	39-40
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	✓	41
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	✓	39
		Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	×	-
		Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	×	-
Blinding (masking)	9	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	×	-
Unit of Analysis	10	Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	✓	39
		If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	×	-
Statistical Methods	11	Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	✓	41
		Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	×	-

		Methods for imputing missing data, if used	×	-
		Statistical software or programs used	✓	41
RESULTS				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	✓	39
		• *Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study*	✓	39
		• *Assignment: the numbers of participants assigned to a study condition*	✓	39
		• *Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention*	✓	39
		• *Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition*	✓	39
		• *Analysis: the number of participants included in or excluded from the main analysis, by study condition*	✓	39
		Description of protocol deviations from study as planned, along with reasons	×	-
Recruitment	13	Dates defining the periods of recruitment and follow-up	✓	38
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	✓	42
		Baseline characteristics for each study condition relevant to specific disease prevention research	✓	42
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	×	-
		Comparison between study population at baseline and target population	✓	42
Baseline equivalence	15	Data on study group equivalence at baseline and statistical methods used to control for baseline differences	✓	42
Numbers analyzed	16	Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	38
		Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	×	-
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	×	-
		Inclusion of null and negative findings	✓	42-43
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	×	-
Ancillary analyses	18	Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	×	-
Adverse events	19	Summary of all important adverse events or unintended effects in each study condition (including summary measures, effect size estimates, and confidence intervals)	×	-
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	43
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	44-45
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	✓	44-45
		Discussion of research, programmatic, or policy implications	✓	45
Generalizability	21	Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study	✓	45
Overall Evidence	22	General interpretation of the results in the context of current evidence and current theory	✓	45

CAPÍTULO 2

Efeitos de fitoestrogênios e anti-hipertensivos nas respostas cardiovasculares ao exercício

ESTUDO 3

ISOFLAVONE DOES NOT PROMOTE ADDITIONAL EFFECTS ON HEART RATE VARIABILITY OF POSTMENOPAUSAL WOMEN PERFORMING COMBINED EXERCISE TRAINING: A CLINICAL, CONTROLLED, RANDOMIZED, DOUBLE-BLIND STUDY

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ABSTRACT

The aim of the study was to investigate the effects of ingesting isoflavones associated with combined aerobic and resistance exercise training on heart rate variability (HRV) indices in postmenopausal women. Twenty-eight healthy postmenopausal women performed 10 weeks of combined exercise training associated with isoflavone (n = 16) or placebo (n = 12) supplementation. The RR intervals (RRi) were collected for 20 min using a heart rate monitor. Analysis of HRV was performed in time (mean squared difference of successive RRi (RMSSD), standard deviation of all normal RRi (SDNN), and percentage of adjacent RRi differing by more than 50 ms (pNN50)), frequency (low-frequency percentage (LF%), high-frequency percentage (HF%), and low-/high-frequency ratio (LF/HF)), and nonlinear domains (standard deviation of the instantaneous variability of the beat-to-beat interval (SD1), long-term variability of the continuous RRi (SD2), and their ratio (SD2/SD1)). Student's t test did not show differences between groups in any general baseline characteristic variables. The results of the generalized estimating equation tests did not demonstrate interaction or group effects for any HRV indices. However, the results reported time effects for mean RR ($p < 0.001$), RMSSD ($p = 0.044$), and SD1 ($p = 0.044$), with increases in these indices in response to exercise training. There were no time effects for LF%, HF%, LF/HF, SDNN, pNN50, SD2, or SD2/SD1. In conclusion, isoflavone supplementation did not promote additional effects on HRV indices of postmenopausal women subjected to 10 weeks of combined exercise training.

Key words: exercise, autonomic, supplementation, climacteric, isoflavones, aerobic, resistance, combined, menopause, heart rate variability.

INTRODUCTION

The inclusion of aerobic and resistance exercises in training programs has been recommended to maintain and improve the health and function of the cardiovascular system and skeletal muscles of young and older adults [1,2]. In postmenopausal women, combined exercise training (CET; aerobic and resistance exercises in the same session) may promote additional effects, which attenuates climacteric symptoms, systemic inflammation markers, and oxidative stress and improves bone health [3,4]. Furthermore, training programs that contain aerobic exercises may improve the heart rate variability (HRV; i.e., a validated measure for evaluating cardiac autonomic modulation [5,6]) in postmenopausal women [6,7]. This improvement in HRV is an important effect as the reduced level of estrogen reported postmenopause may reduce cardiac modulation by the autonomic nervous system [8–10], which is associated with an increased risk of arrhythmia and sudden cardiac death.

Although the effect of therapy with female sex hormones on HRV remains controversial [11,12], there is evidence reporting the role of estrogen in the modulation of the autonomic nervous system [9,13,14]. Indirect and direct mechanisms may be involved in this modulation [9,14,15]. Postmenopausal symptoms such as hot flashes and sleep problems, for example, are associated with altered autonomic control of the heart rate [15]. Previous studies [16,17] show significant decreases in cardiac vagal control during hot flashes in late perimenopausal and postmenopausal women. Furthermore, postmenopausal women exhibited higher basal levels of noradrenaline than premenopausal women [13]. As a direct mechanism, estrogen may act within central nuclei to modulate autonomic function [14], showing a central mediated action of estrogen. In this way, isoflavone has been used as an alternative treatment aiming to reduce postmenopausal symptoms [18,19]. Isoflavone is a phytoestrogen that exhibits a similar chemical structure to estrogen, presenting high affinity to estrogen receptors [19]. This leads us to suggest that isoflavone consumption could provide additional beneficial effects on HRV indices increased by exercise practice. However, understanding of the effects of isoflavone on HRV is limited and it is important to investigate whether isoflavone provides additive effects on HRV in postmenopausal women submitted to CET.

The aim of the present study was to investigate the effects of ingesting isoflavone in addition to CET on HRV indices in nonobese postmenopausal women. The hypothesis raised was that isoflavone would promote additional improvement in HRV indices compared with isolated CET.

METHODS

PARTICIPANTS

A total of 260 postmenopausal women (amenorrhea for at least 12 months) aged 50–70 years were recruited through advertisements in traditional (newspapers, radio, and television) and electronic media (social media), with the provision of a telephone contact for those who were interested. After contact, interviews were scheduled to verify compliance with the following inclusion criteria: able to engage in treadmill and resistance training; no history of cardiovascular disease, diabetes, renal pathologies, or hypertension; nonsmoker; no hormone therapy or isoflavones use for at least 3 years; and signed a consent form. The exclusion criteria were not taking all capsules, not performing the initial or final evaluations, or initiating another exercise protocol concomitant to the study. All volunteers were instructed to maintain their diet and sleep habits throughout the study. The follow-up flowchart is presented in Fig. 1. In total, 36 women who met the inclusion criteria were recruited and allocated (17 on placebo and exercise and 19 on isoflavone supplementation and exercise); of these, 32 completed the protocol and 4 were excluded from the HRV analyses because of bad signal quality, totaling 28 volunteers (12 on placebo and exercise and 16 on isoflavone supplementation and exercise). The sample and interventions used in the present study were the same as those used in a previous study aimed at verifying the effects of CET and isoflavone supplementation on climacteric symptoms in postmenopausal women (Costa et al. 2017). This study was approved by the local ethics committee (Federal University of Uberlândia; CAAE: 40622414.9.0000.5152) and recorded in the international registration of clinical trials at clinicaltrials.gov (identifier no. NCT03008785).

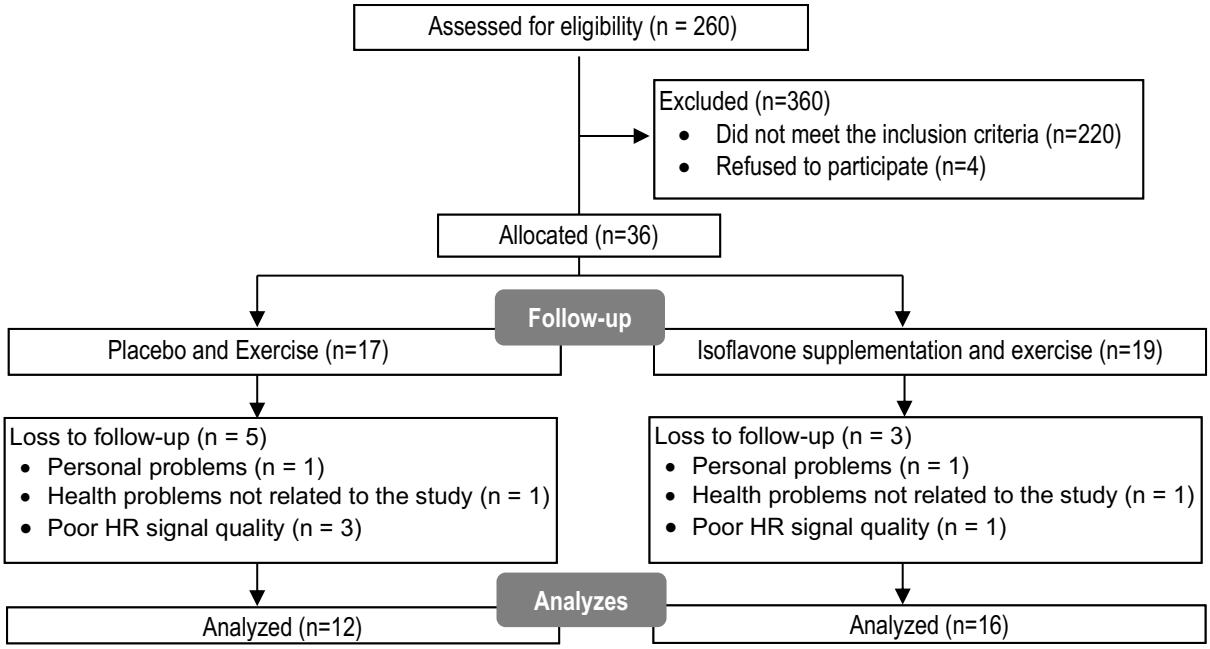

Figure 1 – *Follow-up flowchart. HR: Heart rate.*

STUDY DESIGN

This study is a parallel randomized, double-blinded, placebo controlled clinical trial. Initially, 38 possible samples (in accordance with the sample size calculation and estimated sample loss) were randomly assigned (by electronic software) to the PLA group (n = 19) who received placebo and to the ISO group (n = 19) who received isoflavone supplementation. However, after recruitment, only 36 women met the inclusion criteria and were allocated to the PLA group (n = 17) and the ISO group (n = 19). In association with placebo or isoflavone consumption, participants performed 30 sessions of CET for 10 weeks. Before the first day of training, participants were characterized by anthropometric evaluation and a questionnaire on physical activity level. Furthermore, they performed a treadmill incremental test and a maximal strength test (1 repetition maximum test; 1RM), with an interval of at least 48 h, to determine the intensity of training. HRV was evaluated before and after training, after at least 48 h without exercise. Volunteers were instructed to abstain from alcohol and caffeine. All procedures were performed in the Cardiorespiratory and Metabolic Physiology Laboratory of the Faculty of Physical Education at the Federal University of Uberlândia from February to December 2015.

ANTHROPOMETRIC MEASUREMENTS AND PHYSICAL ACTIVITY LEVEL

The anthropometric evaluations were performed in an isolated environment in the morning after 8 h of fasting. The following variables were measured: body mass, using an electronic scale (Filizola, São Paulo, SP, Brazil); height, using a fixed stadiometer (Sanny, São

Bernardo do Campo, SP, Brazil); abdominal, waist, and hip circumferences, using a 0.5-cm wide inelastic tape (Filizola); and fat mass, using tetrapolar bioimpedance (Biodynamics Model 450c; Biodynamics, Shoreline, Wash., USA). Physical activity level was assessed using the International Physical Activity Questionnaire (IPAQ; Short Version), validated for the Brazilian population [20].

INCREMENTAL TREADMILL TEST

The submaximal incremental treadmill test was performed with a fixed velocity of 5.5 km/h and intensity imposed by the incline (%) to identify exercise intensity between ventilatory thresholds 1 and 2 for exercise prescription. After a 5-min warm-up with a 0% incline, the test began with a 1% incline. The protocol consisted of 2-min stages with 1% increments in incline per stage until the volunteers reached 85% of their predicted maximum heart rate or 18 for the rate of perceived exertion [21]. Oxygen uptake and carbon dioxide output were recorded during the tests using a gas analyzer (Cosmed Quark CPET, Rome, Italy) to identify the ventilatory thresholds based on ventilatory equivalents [22].

1RM TEST

For the 1RM test, participants performed a specific warm-up consisting of the same exercise as the test, with 2 sets at intensities of around 40%–50% and 60%–80% of the subjective estimate of 1RM and with 8–10 and 3–5 repetitions, respectively. After this warm-up, a maximum of 5 attempts were allowed per exercise to find the highest workload at which the participant could only perform 1 complete movement with the correct technique [23]. If the 1RM score was not found in the first session, a new session was scheduled after an interval of at least 48 h. The order of exercises tested was leg press, bench press, lateral pulldown, pec deck, and seated cable row.

COMBINED EXERCISE TRAINING PROGRAM

The training program consisted of combined aerobic and resistance exercises performed 3 times a week in 45-min sessions for 10 weeks. The sessions began with a 5-min warm-up on a treadmill at 5.5 km/h without inclination, followed by 20 min of aerobic exercises and 20 min of resistance exercises. The aerobic training was performed at a velocity of 5.5 km/h with the treadmill inclination corresponding to between ventilatory thresholds 1 and 2 determined in an incremental treadmill test. Intensity increments of 20% were performed in the fifth week of training. Data on volunteers who were absent for more than 15% of training were excluded from the analysis.

The resistance exercises were performed in 2 sets of 15 repetitions, with 30 s between exercises and sets. Seven resistance exercises were performed: leg press 45° (hip and knee extension); chest press in vertical machine (shoulder horizontal abduction and elbow extension); anterior latissimus dorsi pulldown (shoulder abduction and elbow flexion); seated cable row (shoulder extension and elbow flexion); pec deck (shoulder horizontal adduction with flexed elbows); squat with lumbar Swiss ball support (hip and knee extension); and classic abdominal crunch (spine flexion with fixed hip and flexed knee on a flat surface). The resistance exercise intensity corresponded to 60% of 1RM. A new 1RM test was carried out in the fifth week of training for load readjustment.

HEART RATE ANALYSIS

RR intervals (RRi) were collected for 20 min in a seated position, with spontaneous breathing, in a well-lit room using a heart rate monitor (Polar RS800cx, Polar Electro Oy, Kempele, Finland; sampling frequency, 1000 Hz) and without the influence of sensorial stimuli. Heart rate data were transferred to a computer using Polar Pro trainer 5 software (Polar Electro Oy), after which the RRi were visually inspected, and artifacts were replaced by the mean of the adjacent values. Samples were selected from the range of 300 s with the fewest artifacts closest to the time series end, and signals with more than 2% of artifacts were discarded [5]. HRV analyses were performed in time, frequency, and nonlinear domains [5] using validated [24] software (Kubios HRV 3.0.0; University of Kuopio, Kuopio, Finland).

The analyzed time-domain indices included the square root of the mean squared difference of successive RRi (RMSSD), the standard deviation of all normal RRi (SDNN), and the percentage of adjacent RRi differing by more than 50 ms (pNN50). For frequency domain analysis, time series were interpolated at 4 Hz and the linear trend component signal was removed using the smooth prior technique. Next, the signal was multiplied by the Hanning window and a fast Fourier transform of the product was calculated. Thus, spectral bands were calculated through the integral of the power spectral density curve and specified in low (LF: 0.04–0.15 Hz) and high frequencies (HF: 0.15–0.4 Hz), as well as the ratio (LF/HF). Both LF and HF were normalized (percentage of LF (LF%) and HF (HF%), respectively), representing the relative contribution of each component to the total power minus the very-low frequency component. For nonlinear indices the Poincaré plot was analyzed, and the standard deviation of the instantaneous variability of the beat-to-beat interval (SD1) and the long-term variability of the continuous RRi (SD2) were analyzed, along with the ratio (SD2/SD1).

SUPPLEMENTATION

Volunteers took a capsule of isoflavone or placebo every day of the week (including weekends) from the first day to the last day of training, totaling 70 capsules per volunteer during the 10 weeks of training. Every Monday, each volunteer received a plastic refill containing the substances (isoflavone or placebo) with markings for the days. In the initial and final evaluations, volunteers did not receive supplementation. At every training session, participants were reminded and encouraged to maintain supplementation. The ISO capsules contained 100 mg of isoflavone (composition: 3.3% genistein, 93.5% daidzein, and 3.2% glycitein) that was derived from soybean, corresponding to approximately 37.58 g of soy [25], whereas the PLA capsules contained 100 mg of cornstarch. All capsules were identical in appearance, taste, and smell.

STATISTICAL ANALYSIS

The sample calculation was performed using G*Power software (version 3.1.9.2; [26]) and considering RMSSD as the main variable. An a priori f family test for within–between interaction repeated-measures ANOVA was performed, with a possible effect size (*f*) of 0.3, a probability of error α of 0.05, power (1-β) of 0.8, correlation between repeated measures of 0.5, and a nonsphericity correction of 1. Thus, a total sample size (summed of over all groups) of 24 individuals was determined.

The pre- and post-HRV results are presented as means ± SD, variation (Δ), and lower and upper limits of the 95% confidence interval. Normality of data was tested using the Shapiro–Wilk test. Student's t test was used to compare HRV and the general characteristics of participants at the pre-intervention phase, and data are presented as means ± SD. The Mann–Whitney test was performed for variables without normal distribution, and these data are presented as median and interquartile range (25%–75%). Pearson's χ^2 test was used to compare the physical activity level (by IPAQ) between groups, followed by the Monte Carlo test when the expected frequency was less than 5. A 2-factor (time and group) generalized estimating equation technique was performed for between, within, and interaction comparisons. All analyses were performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, N.Y., USA). The significance level adopted was $p < 0.05$.

RESULTS

The IPAQ analyses (data not shown) demonstrated that although no participants practiced regular exercises, none of the women were sedentary. The levels of physical activity

were not different between groups ($\chi^2 = 0.609$; $p = 0.772$). No differences were found between groups at any pre-intervention HRV index (values can be checked in *Table 1*; statistical data not shown). However, there was a significant difference in mean RR values ($p = 0.026$). The general baseline characteristics are presented in *Table 2*. There were no differences between groups in any general baseline characteristic variables.

Table 1 – *Heart Rate Variability*

	Groups	Pre (mean ± SD)	Post (mean ± SD)	Δ (95%CI)	p Group	p Time	p Inter.
Mean RR (ms)	ISO	844.8±84.8	885.4±139.7	40.6 (-7.2 to 88.5)	0.125	<0.001	0.113
	PLA	760.1±104.5	855.3±114.2	95.2 (47.6 to 142.8)			
SDNN (ms)	ISO	25.3±11.0	25.9±10.4	0.6 (-8.1 to 9.4)	0.934	0.172	0.235
	PLA	21.0±14.3	29.7±17.2	8.7 (-1.4 to 18.8)			
RMSSD (ms)	ISO	19.5±10.9	23.1±15.2	3.6 (-5.2 to 12.5)	0.883	0.044	0.338
	PLA	15.6±11.4	25.9±14.9	10.2 (0.1 to 20.4)			
pNN50 (%)	ISO	4.1±7.4	8.0±15.7	3.9 (-3.4 to 11.3)	0.779	0.094	0.769
	PLA	2.4±6.7	8.1±10.5	5.6 (-2.8 to 14.0)			
LF% (n.u.)	ISO	74.3±13.6	71.9±22.2	-2.3 (-13.6 to 8.9)	0.574	0.339	0.672
	PLA	73.7±9.5	67.6±18.2	-6.0 (-19.1 to 6.9)			
HF% (n.u.)	ISO	25.7±13.6	28.0±22.2	2.3 (-8.9 to 13.6)	0.578	0.342	0.674
	PLA	26.3±9.5	32.3±18.1	6.0 (-7.0 to 19.0)			
LF/HF	ISO	4.2±2.9	5.1±5.7	0.9 (-1.5 to 3.4)	0.156	0.760	0.522
	PLA	3.4±1.9	3.1±2.1	-0.3 (-3.2 to 2.5)			
SD1 (ms)	ISO	13.8±7.7	16.4±10.8	2.6 (-3.7 to 8.8)	0.883	0.044	0.337
	PLA	11.1±8.1	18.4±10.5	7.3 (0.1 to 14.5)			
SD2 (ms)	ISO	32.8±14.0	32.0±12.1	-0.7 (-11.9 to 10.5)	0.994	0.295	0.224
	PLA	27.4±18.8	37.3±22.7	9.9 (-3.1 to 22.8)			
SD2/SD1	ISO	2.6±0.8	2.4±0.9	-0.2 (-0.7 to 0.3)	0.322	0.311	0.843
	PLA	2.4±0.6	2.2±0.8	-0.2 (-0.7 to 0.4)			

Values are presented as means ± SD and (95% CI). CI, confidence interval; HF%, high-frequency percentage; inter., interaction; ISO, isoflavone group; LF%, low-frequency percentage; LF/HF, low-/high-frequency ratio; n.u., normalized units; PLA, placebo group; pNN50, percentage of pairs of adjacent RR intervals differing by more than 50 ms; RMSSD, root mean square of the successive differences of RR intervals; SD1, standard deviations of the distances from points to diagonal Y = X of the scattergram; SD2, standard deviations of the distances from points to straight Y = −X + RRmean of the scattergram; SDNN, standard deviation of normal RR intervals.

Table 2 – *General baseline characteristics*

Variable	PLA (n=12)	ISO (n=16)	p
Age (years)	52.6 ± 5.3	56.1 ± 5.5	0.100
Time after menopause (years)	3.0 (1.4-5.8)	4.5 (2.0-12.0)	0.217
Body mass (kg)	63.2 ± 7.5	65.9 ± 8.8	0.413
Height (m)	1.55 ± 0.05	1.58 ± 0.05	0.830
Body mass index (kg/m²)	27.1 ± 2.6	26.4 ± 3.4	0.555
Abdominal circumference (cm)	90.3 (87.3-96.8)	100.5 (84.5-104.3)	0.763
Waist circumference (cm)	81.0 (76.0-86.3)	82.3 (74.7-91.5)	0.561
Hip circumference (cm)	102.3 ± 6.8	103.7 ± 7.3	0.614
Waist-Hip ratio	0.79 ± 0.06	0.78 ± 0.06	0.648
Leg press 1RM (kg)	169.6 ± 32.4	158.2 ± 41.6	0.439
Bench press 1RM (kg)	27.3 ± 4.2	25.0 ± 5.2	0.230
Lat pull down 1RM (kg)	30.0 (25.0-35.0)	30.0 (30.0-33.8)	0.807
Pec deck 1RM (kg)	19.2 ± 5.1	19.5 ± 4.4	0.855
Seated cable row 1RM (kg)	57.1 ± 8.4	56.6 ± 12.1	0.899

Data are presented as means ± SD in variables with normal distribution (p from Students t test) and median with interquartile range (25%–75%) in variables without normal distribution (p from Mann–Whitney test). 1RM, 1-repetition maximum test; ISO, isoflavone group; PLA, placebo group.

Table 1 presents the HRV data. The results of the generalized estimating equation tests did not show interaction or group effects for any HRV indices. However, the results reported time effects for mean RR, RMSSD, and SD1, with an increase in these indices in response to CET. There were no differences between moments for LF%, HF%, LF/HF, SDNN, pNN50, SD2, or SD2/SD1.

DISCUSSION

The present study aimed to investigate if isoflavone promoted additional benefits to HRV indices over those provided by CET in postmenopausal women. Our hypothesis was based on similarity of chemical structure between isoflavone and estrogen and its high affinity to estrogen receptors [19]. When stimulated, estrogen receptors may directly (i.e., acting within central nuclei) or indirectly (i.e., regulation of hot flashes and sleep problems; change in basal level of noradrenaline) modulate autonomic function [9,13–15]. However, the results refuted the hypothesis raised, as only time effects were found, in accordance with studies that did not find any benefits of female sex hormonal therapy on cardiac autonomic modulation [11,12].

Postmenopausal symptoms (such as hot flashes and sleep problems) associated with reduced levels of estrogen are related to decreased autonomic control of the heart rate [15]. A systematic review and meta-analysis of randomized controlled trials concluded that soy isoflavone supplements are significantly more effective than placebo in reducing the frequency

and severity of hot flashes [27]. Therefore, it was speculated that isoflavone supplementation could promote an additive reduction in postmenopausal symptoms occasioned by exercise practices [28,29], and consequently promote an indirect additional effect on HRV. Although hot flashes and sleep disturbance symptoms were not analyzed in the present study, a previous study showed that isoflavone supplementation did not promote additive effects in improving these climacteric symptoms when ingested concomitantly with 10 weeks of CET [29]. Therefore, the speculation made in the present study was not confirmed.

Another hypothesis was that isoflavone could interact with estrogen receptors in central nuclei to modulate autonomic function [14], promoting additive improvement in HRV promoted by CET. Modulation in central areas in response to exercise [30,31], which reduces the response efficiency of isoflavone, may explain the lack of additive effect found in the present study. Furthermore, β-endorphin released during exercise can stabilize thermoregulation and prevent hot flashes [28]. Up to now, no additive effect of isoflavone combined with CET on HRV has been found [29].

The time effects reported in mean RR, RMSSD, and SD1 suggest that CET increased the resting cardiac autonomic modulation of postmenopausal women. Mean RR is suggested as a global parameter of cardiac autonomic control [5]. On the other hand, RMSSD and SD1 are most affected by high-frequency variations in the heart rate, and are used as a marker of cardiac vagal control [5]. Improvement in global or vagal indices of autonomic control of the heart rate in postmenopausal women is an important result due to the elevated risk of cardiovascular disease in this population [8,10,32,33] These results suggest that CET promoted intrinsic and/or central cardiovascular adaptations [30,31], which is in accordance with the supposition made in previous paragraphs.

The lack of a group with only isoflavone supplementation, a group without CET, and evaluation of the amount of isoflavone that appears in the blood could be some limitations of this study. However, as the aim of the current study was to investigate if isoflavone supplementation could have additive effects on the exercise-derived responses in HRV, we believe that our study could help to answer this question. Further studies are needed to investigate other doses of isoflavone and the association of this supplementation with other kinds of exercises.

The class of isoflavone used in the present study may be another limitation. The 3 primary isoflavones found in soy are genistein, daidzein, and glycitein [34]. Apparently, studies that show effects of isoflavone on climacteric symptoms use compounds containing at least 15

mg of genistein [35,36], which is a larger quantity than that used in the present study (3.3 mg). A previous study that used a similar quantity of isoflavone compounds also did not show additive effects on a reduction in climacteric symptoms promoted by CET [29]. However, to date, no studies have investigated the effects of different classes of isoflavone on HRV modulation.

In summary, isoflavone did not promote additional effects on HRV indices of postmenopausal women submitted to 10 weeks of CET. The study was conducted in generally healthy, nonobese women; therefore, the results might not be applicable to other groups receiving treatment with higher potency medication or for longer than 10 weeks. It is also important to note that this result is applicable only for isoflavone supplementation and may not be extrapolated to isoflavone consumption from natural and regular foods.

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CONSORT 2010 - reporting a randomised trial.

Section/Topic	Item	Checklist item	pg
Title and abstract			
Title and abstract	1a	Identification as a randomised trial in the title	52
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	53
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	54
	2b	Specific objectives or hypotheses	54
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	56
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	-
Participants	4a	Eligibility criteria for participants	55
	4b	Settings and locations where the data were collected	55
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	57-59
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	-
	6b	Any changes to trial outcomes after the trial commenced, with reasons	-
Sample size	7a	How sample size was determined	59
	7b	When applicable, explanation of any interim analyses and stopping guidelines	-
Randomisation:			
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	8b	Type of randomisation; details of any restriction (such as blocking and block size)	56
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	56
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	56
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	59
	11b	If relevant, description of the similarity of interventions	59
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	59

	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	-
Results			
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	13b	For each group, losses and exclusions after randomisation, together with reasons	55-56
Recruitment	14a	Dates defining the periods of recruitment and follow-up	56
	14b	Why the trial ended or was stopped	56
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Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	60-61
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	60-61
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	-
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	-
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	-
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	62
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	63
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	61-63
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Registration	23	Registration number and name of trial registry	55
Protocol	24	Where the full trial protocol can be accessed, if available	-
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	63

ESTUDO 4

INFLUENCE OF B-BLOCKERS OR ANGIOTENSIN RECEPTOR BLOCKERS ON CARDIOVASCULAR RESPONSES TO EXERCISE IN HYPERTENSIVE POST-MENOPAUSAL WOMEN: A PILOT STUDY.

Igor M. Mariano, Ana Luiza Amaral, Victor Hugo V. Carrijo, Juliene G. C. Dechichi, Priscila A. Dias, Mateus de L. Rodrigues, Arieli Jaqueline F. da Silva, Thulio M. Cunha, Guilherme M. Puga

Status: não publicado.

ABSTRACT

Background: Specific effects of different antihypertensives interaction with physical exercise are not yet clear. ***Aim***: verify the influence of β-blockers or angiotensin receptor blockers on cardiovascular responses to exercise training in hypertensive post-menopausal women. ***Methods***: 30 postmenopausal women were allocated into: healthy control group (CON; n=6); angiotensin receptor blockers users (ARB; n=13); and β-adrenergic blockers users (BB; n=11). Before and after 12 weeks of combined (aerobic and resistance) moderate-intensity exercise training, volunteers underwent a battery of evaluations that included: heart rate (HR) and its variability (HRV), BP under stress (Cold pressor and Stroop color tests), and ambulatorial BP and its variability. ***Results***: In ambulatorial BP analysis only ARB decreased awake systolic BP ($p = 0.011$; ARB: From 122 ± 11 to 117 ± 9; BB: From 118 ± 7 to 114 ± 5; CON: from 121 ± 7 to 127 ± 11 mmHg). In BP reactivity to stress, there are time effects with post-training decreased reactivity in Stroop color DBP, and cold pressor SBP and DBP in all groups. In BP variability analysis, only BB has significative decreased values in systolic SD24 ($p = 0.007$; ΔARB = -0.4 ± 2.4; ΔBB = -2.1 ± 2.3; ΔCON = 1.4 ± 1.9 mmHg) and SDdn ($p = 0.006$; ΔARB = -0.25 ± 2.00; ΔBB = -2.10 ± 2.31; ΔCON = 0.8± 2.6 mmHg). HRV analysis demonstrated that post-training, only BB decreased LF/HF ($p = 0.001$; ΔARB = 0.2 ± 1.0; ΔBB = -0.7 ± 2.0; ΔCON = 1.6 ± 1.9). ***Conclusion***: ARB seems to present more pronounced responses to combined exercise training in awake ambulatorial systolic BP, while β-blockers users present greater responses in BP variability. Besides that, exercise can mitigate BP reactivity to stress with no differences between groups. Lastly, there were no major differences in HRV.

Key words: Exercise; Blood pressure; Hypertension; Blood pressure variability; Heart rate variability; Autonomic.

INTRODUCTION

Hypertension is characterized by sustained high resting blood pressure (BP) [1], often associated with the risk of cardiovascular events, stroke and kidney disease [2]. With advancing age, differences in BP behavior are observed, with a higher incidence in women after the 5th decade of life [3]. This incidence can be explained by the physiological transition to the non-reproductive phase in women, characterized by estrogen deficiency, alterations in the lipid profile, weight gain, high sedentary indices [4] and onset of cardio metabolic diseases, such as hypertension [3].

Pharmacological and non-pharmacological interventions are widely recommended for hypertensive treatment [1]. Among pharmacological treatments, two extensively prescribed antihypertensive classes are non-vasodilating β-adrenergic blockers (BB) and angiotensin receptor blockers (ARB). The antihypertensive mechanism of BB involves mainly central mechanisms, with blockade of β-adrenergic receptors, which causes a decrease in cardiac output, renin secretion, synaptic catecholamines and baroreceptors adaptations [5]. ARB has more systemic effects, antagonizing AT1 receptors of angiotensin II, causing vasodilation and decreasing aldosterone release and production, which causes sodium and water reabsorption causing BP reductions [5].

Regarding non-medication interventions, it is emphasized that physical exercise training may reduce BP [6], including in postmenopausal women [7,8]. However, few studies have addressed cardiovascular changes after combined aerobic and resistance exercise training [8], even though guidelines [1,5] recommend at least 30 minutes of moderate aerobic exercises associated with resistance exercises. In addition, it should be noted that the exercise acts on several BP regulation mechanisms like those of the aforementioned drugs. In this way, exercise can improve autonomic regulation [9], baroreflex sensitivity and bioavailability of vasodilator agents in hypertensive postmenopausal women [7,8]. Therefore, the effects of exercise and medication hypothetically can interact, may be independent or may depend on some saturated pathway.

Then, the objective of this study was to verify the influence of β-blockers or angiotensin receptor blockers on BP responses (resting BP, 24h ambulatorial BP, and BP variability), besides heart rate variability (HRV) as secondary outcome, to exercise training in hypertensive post-menopause women. Our hypothesis was that the use of BB could attenuate these responses by reducing the absolute workload of exercise by its central chronotropic effects when

comparing with lager systemic responses of the ARB. This information has not yet been described and may influence the choices of combinations between pharmacological and non-pharmacological antihypertensive treatments.

MATERIAL AND METHODS

PARTICIPANTS

Four hundred and seven women volunteered through advertising in electronic and traditional media (Social medias, TV, and radio) from 2016 to 2019. From this register were selected those that fit the following inclusion criteria: 1) women aged between 50 and 70 years; 2) amenorrhea of at least 12 months and [FSH]>40mIU/mL; 3) be able to perform physical exercises; 4) antihypertensive treatment with ARB or BB, without drugs or dose changes for 12 months; 5) no history of other cardiovascular diseases; 6) non-smokers; 7) no diagnosis of Diabetes Mellitus or renal pathologies; 8) do not use menopause hormone therapies; and 9) not having uncontrolled hypertension. Before starting the training program, they presented a medical certificate allowing participation and signed the Consent Form. They were instructed to maintain their eating habits during the study. They were assigned into three groups: healthy controls without medication (CON; n=6), ARB users (ARB; n=13) and BB users (BB; n=11). Those who changed the dose or medication during the study were discarded from the analyzes, as shown in *Figure 1*.

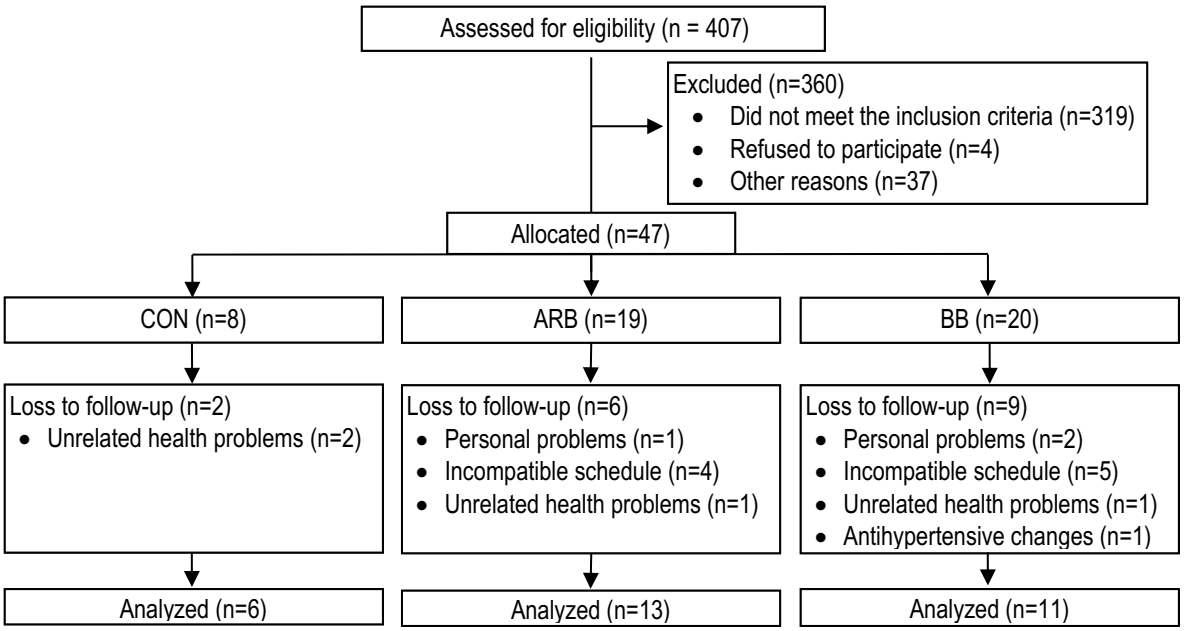

Figure 1 – Follow-up flowchart

GENERAL PROCEDURES

This study was a comparative parallel clinical trial and has international registration of clinical studies in "Clinicaltrials.gov" (nº NCT03529838) and was approved by local Human Research Ethics Committee (40622414.9.0000.5152). Before the intervention, volunteers went through a battery of evaluations that include anthropometry, physical capacity, and cardiovascular measurements. After that, they performed a familiarization with the exercises used in training. Thus, the sessions for strength evaluation (1 repetition maximum test - 1RM) and an incremental treadmill test for aerobic exercise prescription were started. Then, the exercise program was performed three times a week on non-consecutive days for 12 weeks. Between 48 and 96 hours after the end of the training, all evaluations were performed again.

ANTHROPOMETRY

The anthropometric evaluations were performed in an isolated environment, in which are measured: 1) body mass, through an electronic scale (Filizola®, São Paulo, SP, Brazil); 2) height, measured with a fixed stadiometer (Sanny®, São Bernardo do Campo, SP, Brazil); and 3) abdominal circumference, through an inelastic tape measuring 0.5 cm wide (Filizola®, São Paulo, SP, Brazil) placed on the umbilical scar. The evaluation of the body composition was performed through tetra polar bioimpedance (InBody 230 Trepel®; Perafita, Portugal).

CARDIOVASCULAR MEASUREMENTS

Resting BP was monitored through automatic oscillometric monitors (*Omron*® HEM-7113, Shimogyo-ku, Kyoto, Japan) in 3 non-consecutive days. At each measurement day, 3 measurements of systolic BP (SBP), diastolic BP (DBP) and heart rate (HR) were performed and considered as the mean for analysis. The ambulatorial BP measure was performed for 24 hours in pre- and post-training (Dyna Map + Cardios®, São Paulo, SP, Brazil). Such device measured SBP and DBP every 15 minutes between 07:00 and 23:00 and every 30 minutes between 23:00 and 07:00. These values associated with daily report information that they filled while they were with the device, allowed us to evaluate the following BP variability indices: 1) 24h BP standard deviation ($SD24 = \sqrt{\Sigma(BP_x - BP_{mean})^2/n}$); 2) 24h average real variability ($ARV = \Sigma(BP_x - BP_{x-1})/n$); 3) mean diurnal and nocturnal deviations weighted by day and night duration respectively (SDdn). The exam was considered successful when there were at least 80% of valid measures.

To assess BP reactivity to mental stress, we used the 3-minute Stroop protocol [10]. The test consists of images that change every 2 seconds with dissociation between what is written

and the color of the word. The volunteer should then speak as quickly as possible, the color of the letters in the image. So, every minute, BP was measured by auscultatory method. To assess BP reactivity under physical stress, we used the Cold pressor test [11]. The test consists of immersing the volunteers' right hand for 1 minute in water at 4ºC. BP was assessed in the opposite arm after 30 and 60 seconds of immersion using the auscultatory method. In both stress tests, BP reactivity was calculated from the difference between the highest peak during stress and the basal value before it started.

HR was monitored for 20 minutes, seated with spontaneous breathing in complete rest using the POLAR® RS800cx monitor (Kempele, Finland). Data was imported using the Polar Pro trainer 5® software (Kempele, Finland). Thus, data series were visually evaluated, and the artifacts were replaced by the mean of the adjacent values. Series with more than 2% of artifacts were discarded. Thus, we selected the interval with greater stability closer to the end of the sample to analyzes. HRV analyzes were performed using the Kubios® HRV 3.1.0 software (Kuopio, Finland). The considered indices were: 1) RMSSD: square root of the mean of the sums of the square of the differences in adjacent beats; 2) SDNN: standard deviation of all normal beats intervals; 3) high-frequency spectrum (HF; 0.15-0.4Hz) and 4) low-frequency spectrum (LF; 0.04-0.15Hz). LF and HF were expressed in normalized units (n.u.), representing the relative contribution of each component to the total power. The frequency spectrum analysis was performed based on the fast Fourier transform and the linear trend component was removed by the “smooth priors” method.

EXERCISE TRAINING PROGRAM

The exercise training consisted of a combination of aerobic and resistance exercises in the same session, 3 times a week on non-consecutive days for 12 weeks. Each session lasted approximately 60 minutes (30 minutes of aerobic and 30 minutes of resistance exercises). In addition, at each session, the order of the exercises was reversed and monitored through HR monitors and subjective perceived effort scale to ensure safety. All sessions were accompanied by exercise professionals.

The aerobic exercise intensity was determined through an incremental treadmill test with fixed speed at 5.5 km/h, 2-minute stages and 1% of treadmill inclination increments per stage until voluntary exhaustion [12]. This protocol was chosen because it allows to reach maximum parameters without the motor limitation of the running with this population. At the beginning of each aerobic session a 5-minute warm-up on a treadmill with a velocity of 5.5

km/h and 1% of inclination was performed. After that, the aerobic training consisted of walk with fixed speed (5.5 km/h) for 25 minutes and overload imposed by treadmill inclination, aiming to reach the intensity between 65 and 75% of the maximum workload (last completed stage reached in the incremental test). The exercise intensity was increased by 20% after 6 weeks of training.

In order to assess maximum strength in resistance exercises before exercise training, we initially performed 2 familiarizations with the 1 Maximum Repetition test, and then performed the test [13]. The following resistance exercises were performed in the exercise sessions: Leg press 45º (hip and knee extension), Chest press in vertical machine (shoulder horizontal abduction with elbow extension), Anterior latissimus dorsi pulldown (shoulder abduction and elbow flexion), Squat with lumbar Swiss ball support (hip and knee extension), and classic abdominal crunch (spine flexion with fixed hip and flexed knee on a flat surface). Each exercise was performed in a traditional 3-series format of 8-12 repetitions with 60 seconds rest between sets and exercises. The intensity was determined through repetition zones of 8-12 complete movements until there was motor alteration that compromised the correct technique or abrupt reduction in movement speed. The order of the exercises was alternated between agonist muscle groups. The abdominal exercise was performed through maximal repetitions without external load. The load readjustment occurred daily to maintain the repetition zone.

STATISTICAL ANALYZES

The results were presented in mean ± standard deviation. Data normality was assessed using the Shapiro Wilk test and equality of variance using the Levene test. The variables were Log-transformed when they did not meet the requirements of hypothesis testing. To compare the pre-training general characteristics, an independent one factor (Group) ANOVA was used. A two-factor (time and group) ANOVA was used to understand the effects of training and the influence of medications, with Bonferroni post hoc when necessary. Hedges "g" was used to calculate effect sizes. All analyzes were performed using IBM® SPSS® Statistics 21. The significance level was adopted at $p \leq 0.05$.

RESULTS

Table 1 shows general characteristics prior to exercise training. The only significant differences found are that BB has higher triglycerides ($p = 0.019$) and lower maximum HR ($p = 0.001$) than ARB, in addition to lower resting HR ($p = 0.011$) and maximum HR ($p = 0.013$) than CON. All analyzed volunteers performed at least 80% of the sessions.

Table 1 – General baseline characteristics of participants

	CON (n = 6)	ARB (n = 13)	BB (n = 11)	p
Initial Age (years)	61.33 ± 5.43	57.38 ± 5.95	57.09 ± 3.05	0.214
Time after menopause (years)	13.17 ± 6.65	8.51 ± 6.50	8.91 ± 5.84	0.309
Abdominal circumference (cm)	91.00 ± 6.73	96.54 ± 8.95	96.50 ± 9.79	0.410
Body Mass (kg)	66.47 ± 9.79	73.01 ± 9.58	70.15 ± 9.93	0.400
Body Mass Index (kg/m²)	26.48 ± 1.73	29.31 ± 3.82	27.77 ± 4.21	0.285
Fat mass (%)	36.83 ± 3.19	42.38 ± 6.08	39.55 ± 6.67	0.164
[LH] (mUI/MI)	34.06 ± 8.288	46.09 ± 17.18	44.64 ± 21.04	0.371
[FSH] (U/I)	94.46 ± 22.38	82.96 ± 27.17	82.15 ± 34.03	0.674
Total cholesterol (mg/dL)	192.00 ± 36.54	192.31 ± 27.58	184.45 ± 27.41	0.787
HDL (mg/dL)	36.67 ± 7.50	46.38 ± 10.63	38.27 ± 12.17	0.106
LDL (mg/dL)	132.67 ± 33.20	123.92 ± 26.63	110.09 ± 25.96	0.252
Triglycerides (mg/dL)	113.50 ± 39.18	109.54 ± 45.26	180.64 ± 77.85#	0.015
Glycated hemoglobin (%)	5.22 ± 0.33	5.38 ± 0.73	5.55 ± 0.66	0.576
Fasting glucose (mg/dL)	80.33 ± 7.12	83.31 ± 9.78	86.55 ± 8.91	0.392
Resting SBP (mmHg)	112.50 ± 7.57	117.85 ± 12.56	114.91 ± 5.58	0.650
Resting DBP (mmHg)	71.80 ± 6.67	74.42 ± 9.39	71.65 ± 6.36	0.009
Resting HR (bpm)	77.17 ± 7.30	71.99 ± 9.15	64.54 ± 6.03*	0.001
Maximum HR (bpm)	150.66 ± 10.53	152.80 ± 16.13	125.81 ± 17.11*#	0.475
Maximum treadmill inclination (%)	6.83 ± 1.60	8.44 ± 2.93	7.45 ± 3.17	0.838
Leg Press maximum strength (kg)	180.83 ± 24.58	180.38 ± 78.06	194.55 ± 52.56	0.667
Chest Press maximum strength (kg)	27.67 ± 1.97	30.54 ± 6.09	30.91 ± 10.10	0.171
Lat Pulldown maximum strength (kg)	30.83 ± 3.76	32.00 ± 7.07	36.36 ± 6.96	0.214
Losartan	-	7 (54)	-	-
Losartan + Thiazide diuretic	-	6 (46)	-	-
Atenolol	-	-	3 (27)	-
Atenolol + Thiazide diuretic	-	-	5 (45)	-
Propranolol	-	-	3 (27)	-
Statin	-	1 (8)	1 (9)	-
Levothyroxine sodium	1 (17)	5 (38)	1 (9)	-

HR: Heart Rate; [LH]: Luteinizing Hormone concentration; [FSH]: Follicle Stimulating Hormone concentration; HDL: High Density Cholesterol; LDL: Low Density Cholesterol; ARB: Angiotensin receptor blockers users; BB: β-blockers users; CON: Control group. *difference from CON; #difference from ARB. Results presented as "mean ± standard deviation" or "n (%).

Figure 2 represents 24h, awake and sleep ambulatorial BP data. In this analysis, there are no time or groups effect. However, there are interaction effects ($p = 0.011$). Post hoc analysis shows that CON increased awake SBP ($p = 0.048$), and ARB decreased it ($p = 0.016$). BP reactivity to stress tests is represented in *table 2*. In this analysis, there are time effects with post-training decreased reactivity in Stroop color DBP, and Cold pressor SBP and DBP. Besides that, there are group effects, and post hoc analysis revelated that CON is always less reactive than the other groups. There are no interaction effects.

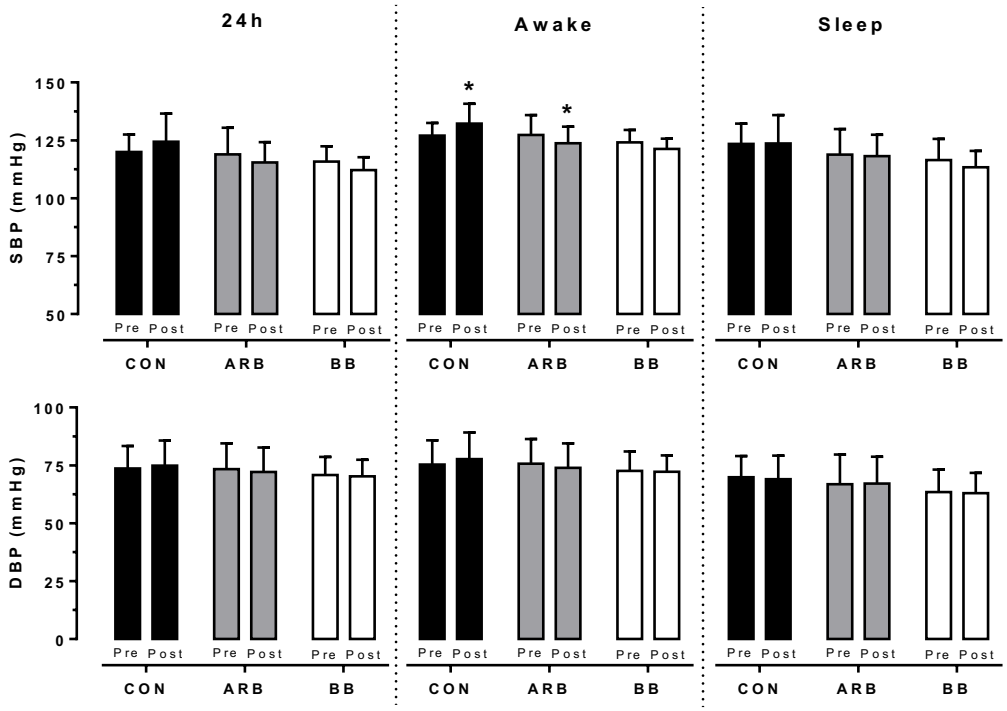

Figure 2 – Ambulatorial blood pressure. SBP: Systolic blood pressure; Diastolic blood pressure; ARB: Angiotensin AT1 receptor blockers users; BB: β-blockers users; CON: Control group; *Difference from pre-exercise training.

Table 2 – *Blood pressure reactivity to stress tests.*

Variable	Group	M ± SD Pre	M ± SD Post	Δ	p Time	p Group	p Inter.	ES
Stroop color								
	CON	33.5 ± 13.3	36.2 ± 18.8	2.7 ± 8.6				0.153
SBP (mmHg)	ARB	34.2 ± 13.2	27.5 ± 13.3	-4.8 ± 16.4	0.221	0.867	0.384	0.490
	BB	37.6 ± 12.5	30.9 ± 13.9	-6.7 ± 13.5				0.488
	CON	18.8 ± 9.0	18.0 ± 12.9	-0.8 ± 11.9				0.066
DBP (mmHg)	ARB	25.3 ± 10.6	18.0 ± 11.5	-6.5 ± 13.7	**0.019**	0.621	0.396	0.639
	BB	24.9 ± 10.6	16.3 ± 9.2	-8.6 ± 8.9				0.833
Cold pressor								
	CON	20.8 ± 12.9	15.7 ± 8.3	-5.2 ± 7.8				0.434
SBP (mmHg)	ARB	34.4 ± 14.5	27.1 ± 13.2	-7.2 ± 19.1	0.050	**0.020**	0.979	0.510
	BB	35.4 ± 12.5	28.7 ± 10.2	-6.7 ± 12.2				0.565
	CON	10.7 ± 4.8	10.0 ± 7.8	-0.7 ± 7.9				0.100
DBP (mmHg)	ARB	26.5 ± 11.6	21.9 ± 11.6	-4.6 ± 10.2	0.021	**0.003**	0.267	0.384
	BB	28.0 ± 7.6	18.3 ± 8.4	-9.7 ± 11.9				1.165

SBP: Systolic blood pressure; Diastolic blood pressure; SD: Standard deviation; ARB: Angiotensin receptor blockers users; BB: β-blockers users; CON: Control group; CI: Confidence interval; Inter.: Interaction; ES: Hedges' g effect size.

Table 3 shows BP and HR variability. In BP variability analysis, there are no time or group significative effects, but there are interaction effects in SBP SD24 and SDdn. Post hoc analysis shows significative decreased values in SBP SD24 (p = 0.007) and SBP SDdn (p =

0.006) only for BB. HRV analysis shows group effects, being that post hoc analysis demonstrated that BB is different from CON in LF (p = 0.048), HF (p = 0.048) and LF/HF (p = 0.024) and ARB is different from CON in LF/HF (p = 0.030). Besides that, post hoc interaction effects analysis demonstrate that BB decreased LF/HF (p = 0.001).

Table 3 – *Blood pressure and heart rate variability.*

Variable	Group	M ± SD Pre	M ± SD Post	Δ	p Time	p Group	p Inter.	ES
Blood pressure variability								
	CON	11.3 ± 1.8	12.7 ± 1.4	1.4 ± 1.9				0.801
SBP SD24 (mmHg)	ARB	12.9 ± 2.4	12.5 ± 1.5	-0.4 ± 2.5	0.436	0.662	**0.023**	0.193
	BB	13.1 ± 2.5	11.0 ± 1.7	-2.1 ± 2.3				0.945
	CON	10.7 ± 1.7	11.5 ± 1.3	0.8 ± 2.6				0.490
SBP SDdn (mmHg)	ARB	11.5 ± 2.0	11.2 ± 1.4	-0.2 ± 2.0	0.302	0.830	**0.041**	0.168
	BB	11.9 ± 2.5	9.8 ± 1.7	-2.1 ± 2.3				0.945
	CON	9.1 ± 1.8	9.5 ± 1.4	0.4 ± 2.2				0.229
SBP ARV (mmHg)	ARB	10.5 ± 2.3	9.8 ± 1.5	-0.6 ± 2.5	0.319	0.671	0.322	0.349
	BB	10.8 ± 2.9	9.1 ± 1.8	-1.6 ± 3.1				0.678
	CON	8.4 ± 2.3	8.9 ± 1.6	0.5 ± 0.9				0.233
DBP SD24 (mmHg)	ARB	9.9 ± 1.6	9.5 ± 1.7	-0.4 ± 2.0	0.552	0.422	0.266	0.235
	BB	10.3 ± 2.7	9.4 ± 1.7	-1.0 ± 1.8				0.384
	CON	7.7 ± 0.8	7.4 ± 1.2	-0.3 ± 0.9				0.271
DBP SDdn (mmHg)	ARB	9.0 ± 1.2	8.5 ± 1.4	-0.4 ± 1.9	0.069	0.156	0.259	0.371
	BB	9.2 ± 1.9	8.0 ± 1.3	-1.2 ± 1.5				0.710
	CON	6.5 ± 1.5	6.2 ± 1.0	-0.2 ± 1.1				0.217
DBP ARV (mmHg)	ARB	7.5 ± 0.9	7.2 ± 1.4	-0.3 ± 1.2	0.193	0.288	0.473	0.247
	BB	8.1 ± 2.9	6.8 ± 1.5	-1.3 ± 3.1				0.542
Heart rate variability								
	CON	19.2 ± 6.0	19.9 ± 9.0	0.7 ± 5.5				0.084
SDNN (ms)	ARB	29.5 ± 16.3	27.0 ± 24.9	-2.5 ± 15.7	1.000	0.341	0.893	0.115
	BB	20.8 ± 6.2	21.5 ± 8.5	0.7 ± 8.3				0.090
	CON	15.0 ± 5.5	14.6 ± 7.2	-0.4 ± 4.3				0.058
RMSSD (ms)	ARB	32.5 ± 27.4	32.7 ± 45.6	0.2 ± 24.1	0.726	0.293	0.938	0.005
	BB	21.7 ± 8.8	24.6 ± 9.8	2.9 ± 11.7				0.299
	CON	66.7 ± 17.3	73.6 ± 16.7	6.9 ± 5.3				0.375
LF (n.u.)	ARB	47.6 ± 22.4	50.9 ± 22.3	3.3 ± 16.2	0.323	**0.032**	0.283	0.143
	BB	47.7 ± 20.8	44.5 ± 13.9	-3.3 ± 14.6				0.174
	CON	33.2 ± 17.3	26.1 ± 16.8	-7.0 ± 4.9				0.330
HF (n.u.)	ARB	52.4 ± 22.4	49.1 ± 22.2	-3.3 ± 16.2	0.317	**0.032**	0.273	0.143
	BB	52.1 ± 20.8	55.4 ± 13.8	3.3 ± 14.6				0.180
	CON	2.5 ± 1.3	4.1 ± 2.7	1.6 ± 1.9				0.697
LF/HF	ARB	1.3 ± 1.3	1.5 ± 1.3	0.2 ± 1.0	0.280	**0.016**	**0.044**	0.149
	BB	1.6 ± 2.2	0.9 ± 0.6	-0.7 ± 2.0				0.418

SBP: Systolic blood pressure; Diastolic blood pressure; SD: Standard deviation; SDdn: SD day and night; ARV: Average real variability; HF: High-frequency; LF: Low-frequency; LF/HF: Low-/high-frequency ratio; n.u.: Normalized units; SDNN: Standard deviation of normal RR intervals; RMSSD: Root mean square of the successive differences of RR intervals; ARB: Angiotensin receptor blockers users and exercise; BB: β-blockers users and exercise; CON: Control group; CI: Confidence interval; Inter.: Interaction; ES: Hedges' g effect size.

DISCUSSION

This study aimed to evaluate BP effects of combined aerobic and resistance exercise training in hypertensive postmenopausal women under BB and ARB use. Our main findings were that ambulatorial BP decreased only in ARB (awake SBP), BP reactivity was mitigated in both groups, CON was less reactive than other groups, and only BB decreased BP variability indices (SBP SD24 and SDdn). Besides that, as secondary outcome, only BB improve LF/HF after exercise training.

Regarding the characteristics of exercise, this training volume (60 minutes/day) was chosen because at moderate intensity it can provide significant BP changes [6]. Despite the hypothesis that BB would perform the aerobic exercises with lower absolute load, this was not confirmed (Maximum load on pre-training: ARB = 8.44 ± 2.93; BB= 7.45 ± 3.17% of inclination) even with the difference in the maximum HR reached in the same test (Maximum HR on pre-training: ARB = 152.80 ± 16.13; BB = 125.81 ± 17.11bpm). Moreover, exercise may act promote diverse indirect and direct cardiovascular benefits in postmenopausal women [7]. Also, the low adherence to drug treatment emphasizes the need for exercise interventions in hypertensive ones [14].

In this sense, exercise training may decrease BP [6], including in hypertensive postmenopausal women [7,8]. Being that, reductions around 5 mmHg of SBP and 2 mmHg of DBP are sufficient to reduce the risk of stroke in 13 and 11.5% respectively [15]. Moreover these reductions can avoid myocardial infarction, stroke and mortality [16]. Considering drug classes, we could not find studies comparing its influence on chronic exercise effects. So, as far as we know, this was the first study to demonstrate differences in BP responses between antihypertensive classes to chronic exercise, improving awake SBP only in ARB. The results for this drug class are supported by studies with a single exercise session, in which intense exercise seems to have independent but additive effects with ARB [17], being greater than the isolated exercise [17,18]. Besides that, angiotensin converting enzyme inhibitors but not ARB mitigates the hypotension that occurs after exercise [19]. No studies in our knowledge described these responses using BB. in relation to other classes, angiotensin converting enzyme inhibitors do not seem to potentiate the hypotensive effects of exercises [20]. With respect to exercise mode, a meta-analysis [6] showed that combined exercise reduce only DBP. In contrast, the present study demonstrated most evident falls in SBP, what it is in consonance with another meta-analysis [21] that found combined exercise as the main strategy for SBP control.

Concerning the possible mechanisms responsible for BP falls, a review of cardiovascular benefits of physical training in hypertensive postmenopausal women [7] describe various of these mechanisms, as: 1) increased baroreflex sensitivity; 2) reduction of autonomic dysfunction, with increase vagal tonus and reduction of sympathetic tone; 3) improvement of endothelial function induced by serum increase of vasodilators; 4) improvements in nitric oxide metabolism, as well as increases in nitrite/nitrate and nitrogen oxide serum concentrations that cause endothelium-dependent vasodilation, reduced vascular resistance and improved arterial stiffness in peripheral arteries, even after combined exercises in this population [8].

Moreover, reductions of BP variability after exercise training in populations with cardiovascular dysfunctions also appear to be promising [22,23] and their results can be independent of BP control [23]. Thus, decreases found in SD24 and SDdn of SBP in the present study are consistent with literature. However, it should be noted that the majority of BP variability studies use aerobic training [22,24] and only few use combined exercise training [23]. Besides that, not just the type, but the exercise intensity seems to be related to the BP variability in a bell-shaped relationship with the best results in moderate intensities [25]. Its effect pathway seems to be more influenced by endothelium and vascular smooth muscle adaptations to training than of sympathetic vasomotor activity variations [25]. The primary role of vessels is also reaffirmed by the consistent results of improvements by pharmacological interventions on BP variability after the use of calcium channel blockers [26–28] for causing significant improvements in vascular compliance by vasodilation [27].

Regarding the BP variability comparison between ARB and BB, our study shows reductions in SBP SD24 and SDdn in BB even if the initial values were similar between groups, what was expected in population with cardio-metabolic diseases after the exercise training [23]. The non-existence of baseline differences between groups is in accordance to a meta-analysis [26], that demonstrates similar effects of these classes of drugs. On the other hand, the vasodilator action of ARB may have saturated the mechanism of action of exercise training, given BP variability apparent vessel-dependent response to exercise [25]. This could explain the improved parameters only in BB. Moreover, the worse vascular health of postmenopausal women [7] could mitigate BP variability response, preventing more pronounced responses even in BB.

In this sense, we did not find any study relating classes of medication with exercise in BP variability, but in an isolated way, drugs present quite diversified results. A robust meta-analysis [26] showed superior results of calcium channel blockers compared to any other class of drugs in decreasing BP variability. Besides that, calcium channel blockers appear to have greater influence on ambulatorial BP variability than ARB [29,30], even if they also show favorable results [31]. Although less consistent, the less promising results seem to be related to BB [26,27], but it is worth emphasizing that a smaller number of studies are performed with this drugs [27]. Another detail worth mentioning is that pharmacological improvements in ambulatory BP variability also appear to be independent of BP reductions [27].

In addition, we demonstrated a reduction in BP reactivity to stressful situations after exercise training, with no difference between groups. This is an important result, as reductions in BP reactivity to stress decrease cardiovascular risk [32]. However, this is not a well-described response pattern, and a meta-analysis found a positive association [33] and another found no association [34] between physical fitness and attenuation of stress reactivity. Regarding the responses to acute exercise, the information seems a little more assertive, demonstrating the ability of combined exercises [35] to mitigate these responses. However, we are unaware of studies comparing different classes of antihypertensive drugs in stress tests after an exercise training phase.

Another evaluation that must be highlighted is the evaluation of autonomic system by HRV [36], since autonomic dysfunctions are both causes and consequences of hypertension [37]. This analyses has shown promising results of exercise interventions in several types of cardiometabolic diseases [9]. However, in the present study, the proposed training only caused improvement of LF/HF in BB. In this context, a meta-analysis [38] on the effects of physical training on HRV, gave evidence that longer training periods (over 12 weeks) have a greater effect. Furthermore, it indicates that these responses have a negative correlation with age [38]. Besides that, there are indications that female sex hormones influence HRV [39,40], decreasing vagal [41] and general parameters [40] and that some specific characteristics of this population can alter HRV, such as: the use of exogenous estrogens [39,42] and presence of vasomotor symptoms [43]. Therefore, the short duration of the training (12 weeks), the use of a middle-aged to elderly population, the climacteric phase and the non-use of hormone therapies may have mitigated adaptations to exercise in the present study.

The present study presents some limitations, such as: few volunteers, existence of polytherapies and the non-standardization of doses and active principles. In this sense, although there are no 3rd generation BB users for having additional vasodilatory effects, there were propranolol users, and since it is non-selective drug, could induce more systemic responses than atenolol users. Although, we did not detect differences in their response patterns in relation to the rest of the group. On the other hand, some characteristics minimized these limitations, such as: there were no differences in number of polytherapies, anthropometric and BP characteristics between groups at baseline and they all took the same drug and dosage for at least 1 year to be adapted to the drug effects. Besides that, achieved power analysis calculations (*Supplement table 1*) demonstrate great power analysis for BP reactivity and HRV frequency domains analysis, but time domain has low power. Ambulatorial BP and BP variability analysis are mixed between great and low achieved power.

The early interruption caused by the COVID-19 pandemic turned this into a pilot study, but it brought important information that may guide new studies, such as: moderate intensity combined exercise may be a good strategy to maintain cardiovascular health in hypertensive postmenopausal women, and especially that BP variability responses can be more pronounced in BB than ARB. These differences, even if marginal, indicate that there may be differences in chronic responses to exercise depending on the drugs classes. With the future deepening of this research area, we may be able to plan interventions with individualized exercises in synergy with drug treatment. However, this is an incipient response and further studies are needed to elucidate the influence of various classes of antihypertensive drugs on exercise responses.

CONCLUSION

Angiotensin receptor blockers users present more pronounced responses to combined exercise training in awake ambulatorial systolic blood pressure, while β-blockers users present greater responses in blood pressure variability. Besides that, exercise can mitigate blood pressure reactivity to stress with no differences between groups, attenuating hypertensive peaks. Lastly, there were no major differences in heart rate variability.

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SUPPLEMENTS

Supplement table 1 – *Achieved power analysis.*

Variable	Time	Group	Interaction
Ambulatorial blood pressure			
SBP 24h	0.71	0.91	1.00
SBP awake	0.45	0.95	1.00
SBP sleep	0.71	0.82	0.52
Blood pressure reactivity			
SBP Stroop color	0.92	0.10	0.93
DBP Stroop color	1.00	0.25	0.92
SBP Cold pressor	1.00	0.99	0.07
DBP Cold pressor	1.00	1.00	0.98
Blood pressure variability			
SBP SD24	0.56	0.22	1.00
SBP SDdn	0.81	0.12	1.00
SBP ARV	0.78	0.22	0.96
DBP 24h	0.22	0.27	0.87
DBP awake	0.10	0.27	1.00
DBP sleep	0.15	0.51	0.06
DBP SD24	0.37	0.43	0.98
DBP SDdn	1.00	0.79	0.99
DBP ARV	0.95	0.59	0.85
Heart rate variability			
SDNN	0.05	0.53	0.19
RMSSD	0.16	0.59	0.12
LF	0.77	0.98	0.98
HF	0.78	0.98	0.98
LF/HF	0.84	0.99	1.00

SBP: Systolic blood pressure; Diastolic blood pressure; SD: Standard deviation; SDdn: SD day and night; ARV: Average real variability; HF: High-frequency; LF: Low-frequency; LF/HF: Low-/high-frequency ratio; SDNN: Standard deviation of normal RR intervals; RMSSD: Root mean square of the successive differences of RR intervals.

TREND statement checklist
(Transparent Reporting of Evaluations with Non-randomized Designs)

Paper Section/ Topic	Item No	Descriptor	Reported? ✓	Reported? Pg
TITLE AND ABSTRACT				
Title and Abstract	1	Information on how unit were allocated to interventions	✓	69
		Structured abstract recommended	✓	69
		Information on target population or study sample	✓	69
INTRODUCTION				
Background	2	Scientific background and explanation of rationale	✓	70
		Theories used in designing behavioral interventions	✓	70
METHODS				
Participants	3	Eligibility criteria for participants, including criteria at different levels in recruitment/sampling plan (e.g., cities, clinics, subjects)	✓	71
		Method of recruitment (e.g., referral, self-selection), including the sampling method if a systematic sampling plan was implemented	✓	71
		Recruitment setting	✓	71
		Settings and locations where the data were collected	✓	72
Interventions	4	Details of the interventions intended for each study condition and how and when they were actually administered, specifically including:	✓	73-74
		• *Content: what was given?*	✓	73
		• *Delivery method: how was the content given?*	✓	73
		• *Unit of delivery: how were the subjects grouped during delivery?*	×	-
		• *Deliverer: who delivered the intervention?*	×	-
		• *Setting: where was the intervention delivered?*	✓	72
		• *Exposure quantity and duration: how many sessions or episodes or events were intended to be delivered? How long were they intended to last?*	✓	73
		• *Time span: how long was it intended to take to deliver the intervention to each unit?*	✓	73
		• *Activities to increase compliance or adherence (e.g., incentives)*	×	
Objectives	5	Specific objectives and hypotheses	✓	70-71
Outcomes	6	Clearly defined primary and secondary outcome measures	✓	70-71
		Methods used to collect data and any methods used to enhance the quality of measurements	✓	72-73
		Information on validated instruments such as psychometric and biometric properties	✓	72-73
Sample Size	7	How sample size was determined and, when applicable, explanation of any interim analyses and stopping rules	×	-
Assignment Method	8	Unit of assignment (the unit being assigned to study condition, e.g., individual, group, community)	✓	72
		Method used to assign units to study conditions, including details of any restriction (e.g., blocking, stratification, minimization)	✓	71
		Inclusion of aspects employed to help minimize potential bias induced due to non-randomization (e.g., matching)	✓	71
Blinding (masking)	9	Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to study condition assignment; if so, statement regarding how the blinding was accomplished and how it was assessed.	×	-
Unit of Analysis	10	Description of the smallest unit that is being analyzed to assess intervention effects (e.g., individual, group, or community)	✓	71
		If the unit of analysis differs from the unit of assignment, the analytical method used to account for this (e.g., adjusting the standard error estimates by the design effect or using multilevel analysis)	×	-
Statistical Methods	11	Statistical methods used to compare study groups for primary methods outcome(s), including complex methods of correlated data	✓	74
		Statistical methods used for additional analyses, such as a subgroup analyses and adjusted analysis	×	-

		Methods for imputing missing data, if used	×	-
		Statistical software or programs used	✓	74
RESULTS				
Participant flow	12	Flow of participants through each stage of the study: enrollment, assignment, allocation, and intervention exposure, follow-up, analysis (a diagram is strongly recommended)	✓	71
		• *Enrollment: the numbers of participants screened for eligibility, found to be eligible or not eligible, declined to be enrolled, and enrolled in the study*	✓	71
		• *Assignment: the numbers of participants assigned to a study condition*	✓	71
		• *Allocation and intervention exposure: the number of participants assigned to each study condition and the number of participants who received each intervention*	✓	71
		• *Follow-up: the number of participants who completed the follow-up or did not complete the follow-up (i.e., lost to follow-up), by study condition*	✓	71
		• *Analysis: the number of participants included in or excluded from the main analysis, by study condition*	✓	71
		Description of protocol deviations from study as planned, along with reasons	×	-
Recruitment	13	Dates defining the periods of recruitment and follow-up	✓	71
Baseline Data	14	Baseline demographic and clinical characteristics of participants in each study condition	✓	75
		Baseline characteristics for each study condition relevant to specific disease prevention research	✓	76-77
		Baseline comparisons of those lost to follow-up and those retained, overall and by study condition	×	-
		Comparison between study population at baseline and target population of interest	✓	76-77
Baseline equivalence	15	Data on study group equivalence at baseline and statistical methods used to control for baseline differences	✓	75
Numbers analyzed	16	Number of participants (denominator) included in each analysis for each study condition, particularly when the denominators change for different outcomes; statement of the results in absolute numbers when feasible	✓	75
		Indication of whether the analysis strategy was "intention to treat" or, if not, description of how non-compliers were treated in the analyses	×	-
Outcomes and estimation	17	For each primary and secondary outcome, a summary of results for each estimation study condition, and the estimated effect size and a confidence interval to indicate the precision	×	-
		Inclusion of null and negative findings	✓	76-77
		Inclusion of results from testing pre-specified causal pathways through which the intervention was intended to operate, if any	×	-
Ancillary analyses	18	Summary of other analyses performed, including subgroup or restricted analyses, indicating which are pre-specified or exploratory	×	-
Adverse events	19	Summary of all important adverse events or unintended effects in each condition (including summary measures, effect size estimates, and confidence intervals)	×	-
DISCUSSION				
Interpretation	20	Interpretation of the results, taking into account study hypotheses, sources of potential bias, imprecision of measures, multiplicative analyses, and other limitations or weaknesses of the study	✓	78
		Discussion of results taking into account the mechanism by which the intervention was intended to work (causal pathways) or alternative mechanisms or explanations	✓	78-81
		Discussion of the success of and barriers to implementing the intervention, fidelity of implementation	✓	78-81
		Discussion of research, programmatic, or policy implications	✓	81
Generalizability	21	Generalizability (external validity) of the trial findings, taking into account the study population, the characteristics of the intervention, length of follow-up, incentives, compliance rates, specific sites/settings involved in the study	✓	81
Overall Evidence	22	General interpretation of the results in the context of current evidence and current theory	✓	81

CAPÍTULO 3

Efeitos meta-analíticos do exercício nos picos hipertensivos sob estresse

ESTUDO 5

A SINGLE SESSION OF EXERCISE REDUCES STRESS-INDUCED BLOOD PRESSURE: A SYSTEMATIC REVIEW WITH META-ANALYSIS.

Igor M. Mariano, Ana Luiza Amaral, Paula A. B. Ribeiro, Guilherme M. Puga

Status: não publicado.

ABSTRACT

Background: Stressful situations are common in everyday life and disturb the homeostasis. So, an exercise session is a possible strategy to mitigate blood pressure (BP) peaks in response to stressful situations (i.e. BP reactivity), decreasing the cardiovascular risk of these individuals. **Aim:** Verify the effects of a single session of physical exercises on BP reactivity to stress. **Methods**: This is a systematic review with meta-analysis that examined the effect of an exercise session on BP reactivity in responses to laboratory stressor tasks in adults. The searches were realized in digital databases (PUBMED, LILACS, EMBASE and PsycInfo) and 28 studies were included, totaling 846 individuals (meta-analysis stage: k = 24 and n = 710). **Results**: As for exercise characteristics, 2 included interventions with Yoga, 3 resistance exercises, 1 combined exercise, and 23 focused on aerobic exercises. In addition, 24 of the 28 studies focused on low to moderate intensities. Favorable metanalytic results (standardized mean differences through random effects approach) for the exercises were found, with attenuated reactivity in systolic BP (mean effect size = -0.35 [-0.46; -0.23], representing average reductions of 3.8 ± 3.5 mmHg), diastolic BP (mean effect size = -0.49 [-0.68; -0.30], representing average reductions of 3.1 ± 3.6 mmHg), and mean BP (mean effect size = -0.48 [-0.70; -0.26], representing average reductions of 4.1 ± 3.0 mmHg). **Conclusions**: Acute physical exercise lowers systolic, diastolic, and mean blood pressure reactivity in response to stressor tasks.

Key Words: Aerobic Exercise; Resistance Exercise; Blood Pressure; Stress; Reactivity.

INTRODUCTION

Stressful situations are common in modern life and can cause alterations in autonomic, catecholaminergic and neural networks in response to it [1–3]. In this way, simple laboratory stress tests that disturb the homeostasis in a controlled manner, was previously associated with development of future cardiovascular events, depression and decreased telomere length [4]. This is accomplished through different types of stressors, such as: physical (e.g. cold), mental (e.g. arithmetic task) or a mix of both [5]. To assess these responses, several markers are used [5], of which we will highlight the blood pressure (BP) alterations (i.e. hypertensive peaks).

In a broad context, high BP is one of the main preventable factors associated with premature death globally [6] and is associated with the risk of cardiovascular events, strokes and kidney disease [7]. In this way, one of BP's control strategies is to perform physical exercises. Evidence shows that even after a single exercise section, BP can be below baseline levels at rest [8] but its influence on BP reactivity to stressful situations is still poorly understood. Despite that, it has already been suggested that cardiovascular responses to stress are better indicators of left ventricular mass [9] and the development of hypertension [10,11] then resting BP, reiterating the importance of studying these responses.

In 2006, a meta-analysis by Hamer and collaborators [12] evaluated the acute effects of aerobic exercise on BP reactivity to stress and found favorable results with attenuated hypertensive peaks. However, in addition to new studies being produced since then, responses to non-aerobic exercise are still unclear. Thus, the aim of the present systematic review with meta-analysis is to verify the acute effects of physical exercise on stress related BP reactivity in adults. The hypothesis is that the exercise will be able to mitigate these responses.

METHODS

This systematic review with meta-analysis followed PRISMA guidelines [13,14], had its protocol previously published [15] and was registered on “PROSPERO” (CRD42020194353).

ELIGIBILITY CRITERIA

Studies with the following characteristics were eligible: 1) Population: human, both sexes, adults (i.e. >18 years), regardless of health or training status; 2) Intervention: a session of physical exercise; 3) Control: a session without exercise; 4) Outcome of interest: BP reactivity under stress (peak BP during stress test or BP variation from basal levels); 5) Languages: English, Portuguese or Spanish; 6) Study designs: randomized clinical trials or

crossovers; 7) Publication dates: no time limit; 8) Other characteristics: in studies with more than two intervention arms, only comparisons with the control group were considered, dividing the control sample proportionately in order to avoid sample duplication in the final analysis

SEARCH STRATEGY

The searches were performed on March 17th/2021, in digital databases (PUBMED, LILACS, EMBASE and PsycInfo). Also, in the reference lists of the included studies, and through manual search in other websites ("https://core.ac.uk/" and "https://scholar.google.com/"). The search was organized into the following categories of terms: exercise intervention, BP and stressors. Parentheses and Boolean operators were used to organize the terms. All included terms are shown in the *Supplement table 1* and the flow diagram is show in *figure 1*.

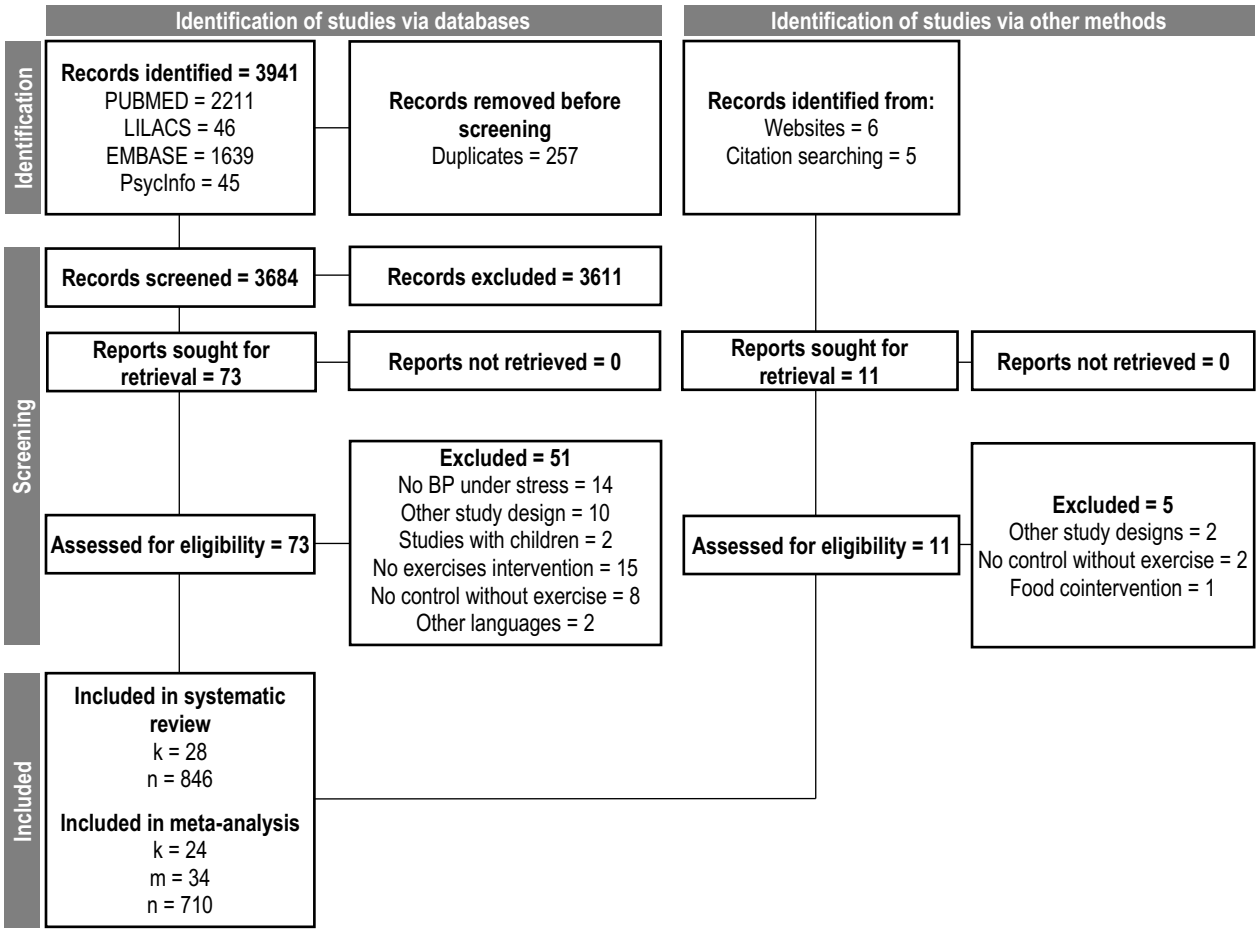

Figure 1 – *Flow diagram. k: number of studies, n: pooled sample size, BP: blood pressure.*

SCREENING AND DATA EXTRACTION PROCESS

During the process of screening (title and abstract, and full text stages), data extraction and risk of bias assessment, the studies were evaluated in duplicate by independent reviewers.

After checking the responses, the reviewer's disagreements were resolved by consensus or by a third reviewer when necessary. The reviewer's agreement was estimated from Cohen's kappa in both full text screening ($\kappa = 0.631$; $p < 0.001$) and risk of bias assessment stages ($\kappa = 0.877$; $p < 0.001$). Before data extraction phase, one of the reviewers standardized codes for all studies included in following analyzes. Thus, each reviewer independently filled an electronic datasheet detailing the characteristics of the studies and the data was compared to assess agreement and identify errors. This datasheet included: identification code, author last name, publication year, language, study design, participants sexes and respective sample sizes, participants health and fitness status, age, hypertension status, other comorbidities, other relevant participants characteristics, exercise intensity, exercise volume (measured in minutes), exercise mode (aerobic, resistance, combined or yoga), stressor test, BP measure device/technique, and BP reactivity measures (sample sizes, mean and standard deviation. If other types of measures were reported, the mean and standard deviation were requested from the authors and in case of null or negative answer the results were transformed when possible). When there was not sufficient data for meta-analysis, the authors were contacted requesting these data. Studies in which the data are presented without numerical description, it was extracted through a web-based software (https://automeris.io/WebPlotDigitizer).

STATISTICAL ANALYSIS

Pooled estimates were calculated using standardized mean differences (SMD) with confidence intervals (95% CI), using "R" programming language through the supplements "meta" [16] and "metafor" [17]. In studies with multiple stressors, we used the mean and pooled dispersion between the stressors. The heterogeneity was measures by Kendall's tau and I^2. Due to the different characteristics of interventions, population, and stress tests, we selected a random effects approach using the Hunter Smith method to summarize the metanalytic results.

The sensitivity analysis was done through the search for outliers and influential points using externally standardized residuals, difference in fits, covariance ratio and Cook's distance methods. In addition, subgroup analyzes by type of stressor, number of stressors, participants sexes, exercise mode, and studies design were made. The individual study assessment of risk of bias was conducted through "Risk of Bias 2.0" [18] and its graphical visualization by the "R" supplement "robvis" [19]. Publication bias analyzes was carried out through Egger's regression and Beggs asymmetry tests, and trim and fill funnel plots.

RESULTS

QUALITATIVE RESULTS

Studies included 425 women, 401 men, and 20 individuals in which sex was not disclosed. In addition, of the 28 studies, only 3 (11%) included hypertensive patients, 21 (75%) had a mean age of less than 30 years, 4 (15%) were from 30 to 40 years old, and only 3 (11%) were over 40 years old. As for stress tests, we have as the most frequent the Stroop color and word test (13 studies), followed by cold pressor and arithmetic test (9 studies each), public speaking (3 studies), hand grip (2 studies), and Trier Social Stress Test, anger- recall interview, and study task (1 study each).

As for exercise characteristics, 2 studies included intervention with Yoga (7%), 3 (11%) with resistance exercises and only 1 (4%) with combined exercises, all the others focused on aerobic exercises. Furthermore, the exercise sessions lasted between 3 and 120 minutes (average of 30-60 minutes). As for intensity, 1 study used self-selection, 3 used high intensity and all others used low to moderate intensity (50-85% of the individual maximum).

Regarding experimental designs, 6 (22%) studies used randomized clinical trial approach, and 22 (78%) adopted a crossover design. As the main results, 11 (39%) studies demonstrated improvements in SBP, 13 (46%) in DBP, and 7 (out of 11; 64%) in MBP. The others had null results since no study has shown harmful BP reactivity effects of exercise. Besides that, four studies did not present data dispersion measures to be included in the meta-analysis [20–23]. The general characteristics of all studies are shown in *table 1*.

Table 1 – *Studies characteristics.*

Study	Population	Stress test	Exercise	Reactivity results
[24]*	NT, 23 women + 17 men, 22 years, athletes	Arithmetic + Stroop color + Public speech	Aerobic (Maximum incremental test)	↓MBP
[25]	NT, 11 women + 13 men, 22 years	Arithmetic	Yoga (30min)	↔SBP ↔DBP
[26]	Borderline HT, 8 participants, 41 years	Stroop color	Aerobic (treadmill, 60min, 60% VO_{2max})	↓SBP ↓DBP ↓MBP
[27]*	NT, 24 men, 22 years	Cold pressor + Stroop color + Public speech	Aerobic (60min or 120min, 55% VO_{2max})	Cold pressor: ↓SBP ↓DBP Other tests: ↔SBP ↔DBP
[28]	NT, 30 men, 21 years	Stroop color	Aerobic (20min, 75-85% $HR_{reserve}$)	↔SBP ↔DBP
[29]	NT, 9 women, 25 years	Cold pressor	Yoga or Aerobic (20min, auto select intensity)	↔SBP ↔DBP
[30]	NT, 10 women + 10 men, 33 years	Cold pressor	Combined (30min, 75-85% HR_{max} and 50% 1RM)	↓SBP ↓DBP
[31]	NT, 7 men, 23 years	Hand grip + Stroop color	Aerobic (120min, 50% VO_{2max})	↔SBP ↔DBP
[32]	NT, 12 men, 23 years	Cold pressor + Stroop color	Aerobic (treadmill, 30min, 60% VO_{2max})	Stroop Color: ↓SBP ↓DBP ↓MBP Cold pressor: ↔SBP ↔DBP ↔MBP
[33]	NT, 48 women, 25-40 years	Stroop color + Public speech	Aerobic (40min, 70% $HR_{reserve}$)	↓SBP ↓DBP ↓MBP
[34]	NT+HT, 18 women + 14 men, 47-51 years	Arithmetic + Cold pressor	Aerobic (20min, 60-70% HR_{max})	↔SBP ↓DBP ↔MBP
[35]	NT, 42 women + 48 men, 23 years	Arithmetic	Aerobic (30min, 50-55% VO_{2max} or 75-80% VO_{2max})	Both intensities: ↓SBP ↓DBP
[36]	NT, 6 women + 9 men, 26 years	Cold pressor	Resistance (30min, 40-60% 1RM)	↔SBP ↓DBP
[37]	NT, 18 men, 20 years	Arithmetic	Resistance (Eccentric movement, 45min, 120% 1RM)	↔SBP ↔DBP
[38]	NT, 24 women (11 smokers), 21 years	Cold pressor + Stroop color	Aerobic (30min, 50% VO_{2peak})	↔SBP ↔DBP ↔MBP
[39]	NT+HT, 12 women + 18 men, 41 years	Stroop color	Aerobic (53min, 50% VO_{2peak})	↓SBP ↓DBP
[40]	NT, 11 men, 25 years	Arithmetic	Aerobic (30min, 70% HR_{max})	↔SBP ↔DBP ↔MBP
[41]*	NT, 80 women, 18 years	Stroop color	Aerobic (10min or 25min or 40min, 70% $HR_{reserve}$)	↔SBP ↓DBP ↓MBP
[42]	NT, 12 participants, 31 years	Stroop color	Aerobic (30min at 50% VO_{2max} or 60min at 80% VO_{2max})	50%: ↔SBP ↓DBP ↓MBP 80%: ↓SBP ↓DBP ↓MBP
[43]	NT, 9 men, 32 years	Hand grip + Stroop color + Arithmetic	Aerobic (30min, 60% VO_{2max})	↔SBP ↔DBP
[44]	NT, 22 women + 4 men, 29 years	Stroop color	Aerobic (Maximum incremental test)	↓SBP ↔DBP ↔MBP
[45]	NT, 22 men, 23 years	Cold pressor	Aerobic (30min at 50-60 $HR_{reserve}$ or 20min interval (4x3min/2min) at 80-90% $HR_{reserve}$)	↔SBP ↔DBP

[46]*	NT, 52 women + 27 men, 22 years	Anger-recall interview	Aerobic (3min, walking)	↔SBP ↔DBP
[47]	NT, 40 men, 26 years	Cold pressor	Resistance (30min or 50min at 70% 1RM)	30min: ↔SBP ↔DBP ↔MBP 50min: ↓SBP ↓DBP ↓MBP
Included only in qualitative analysis				
[20]*	NT, 15 men, 21 years	Arithmetic	Aerobic (Cycle, 20min at 25 or 100 watts)	25 watts: ↔SBP ↔DBP 100 watts: ↓SBP ↓DBP
[21]	NT, 18 women, undergraduate	40 minutes of study	Aerobic (40min at 60-80% HR_{max})	↔SBP ↔DBP
[22]*	NT, 40 women + 40 men, 21 years	Arithmetic	Aerobic (20min at moderate intensity)	↔SBP ↔DBP
[23]	NT, 10 women + 13 men, 24 years	Trier Social Stress Test	Aerobic (30min, 70% VO_{2peak})	↔SBP

*The age refers to the average. SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure; HR: heart rate; HT: hypertensives; NT: normotensives; *: randomized clinical trials, the other studies are cross over designs.*

META-ANALYSIS RESULTS

Among 24 studies included in meta-analysis, 8 presented multiple possible comparisons according to the exercise mode [29], exercise volume [27,41,47], exercise intensity [42,45], parents smoking habit [28], or participants smoking habit [38]. Besides that, 22 studies demonstrate results for SBP (32 comparisons), 23 for DBP (33 comparisons) and 11 for MBP (16 comparisons). The forest plots of SBP, DBP and MBP reactivity are present in *figures 2,3 and 4,* respectively. We found favorable results to exercise in both SBP (Effect size = -0.35 [-0.46; -0.23], representing average reductions of 3.8 ± 3.5 mmHg), DBP (Effect size = -0.49 [-0.68; -0.30], representing average reductions of 3.1 ± 3.6 mmHg) and MBP reactivity (Effect size = -0.48 [-0.70; -0.26], representing average reductions of 4.1 ± 3.0 mmHg). We also highlight that 20 of the studies were carried out in healthy non-athlete individuals aged up to 40 years. Thus, by isolating the analyzes for this population, we maintain the results like the above for SBP (Effect size = -0.30 [-0.43; -0.18]), DBP (Effect size = -0.43 [-0.61; -0.25]), and MBP (Effect size =-0.37 [-0.54; -0.20]).

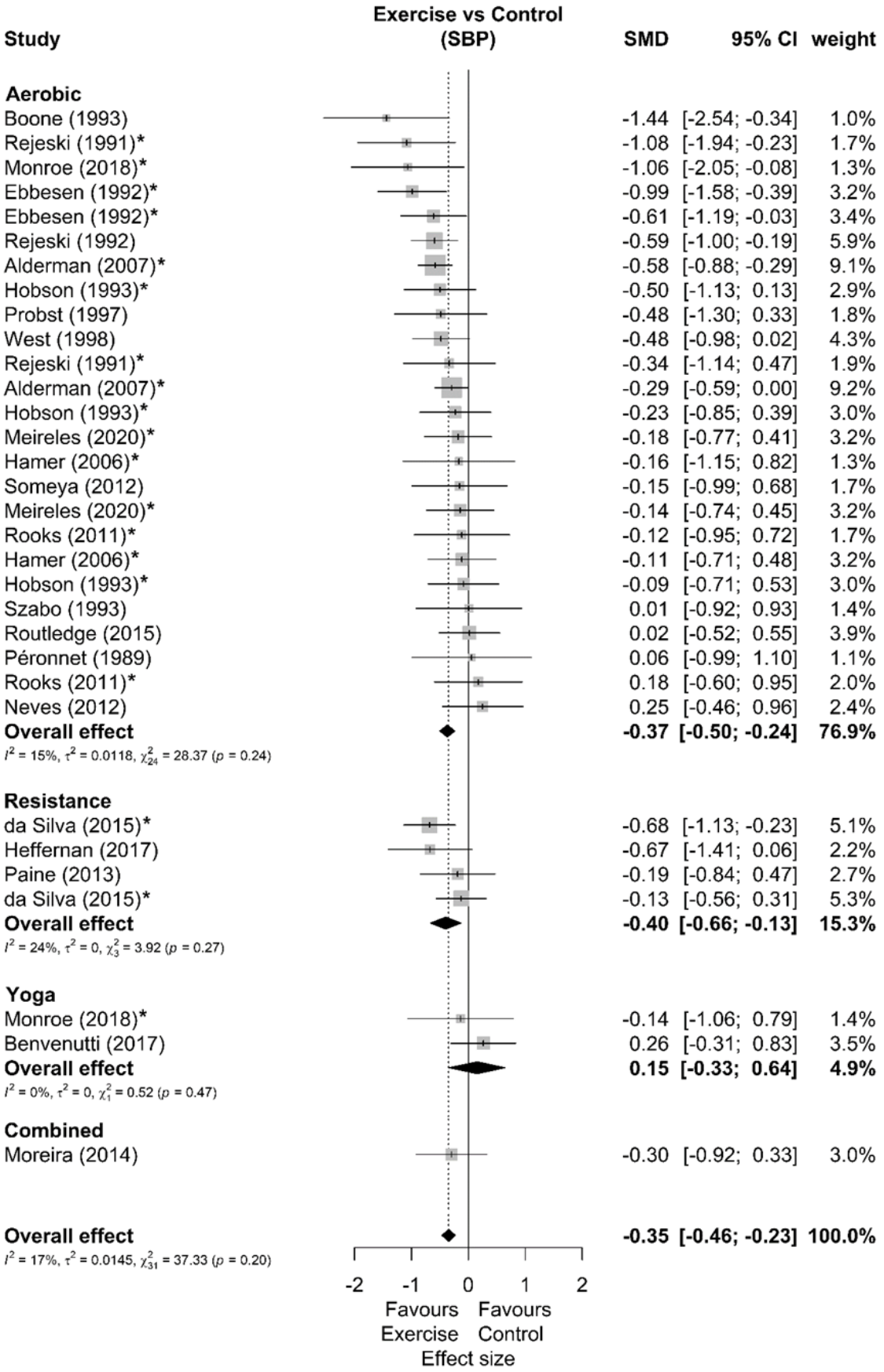

Figure 2 – *Systolic blood pressure reactivity forest plot. SMD: standardized mean difference; SBP: systolic blood pressure; CI: credible interval; *: studies with multiple comparisons.*

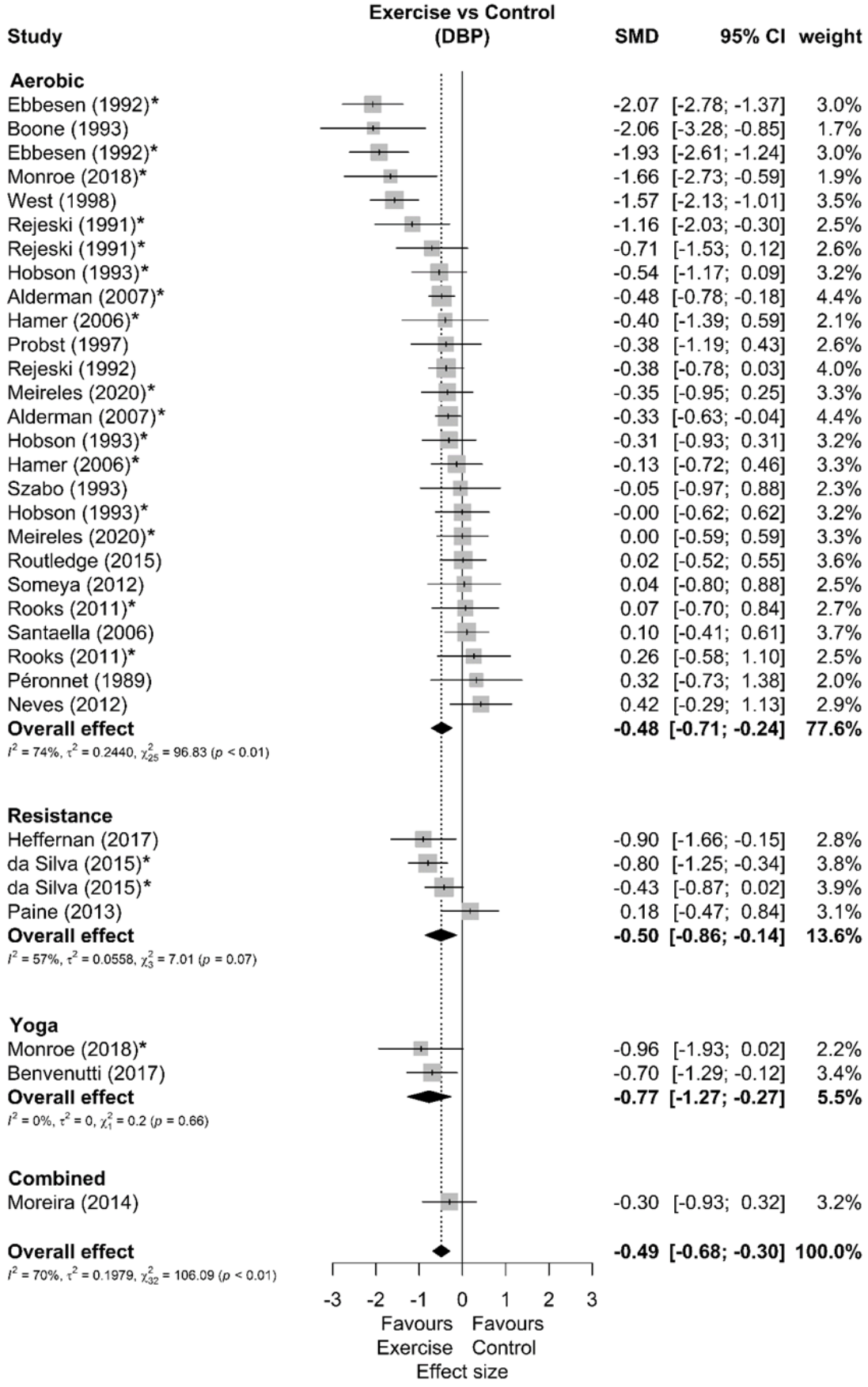

Figure 3 – *Diastolic blood pressure reactivity forest plot. SMD: standardized mean difference; DBP: diastolic blood pressure; CI: credible interval; *: studies with multiple comparisons.*

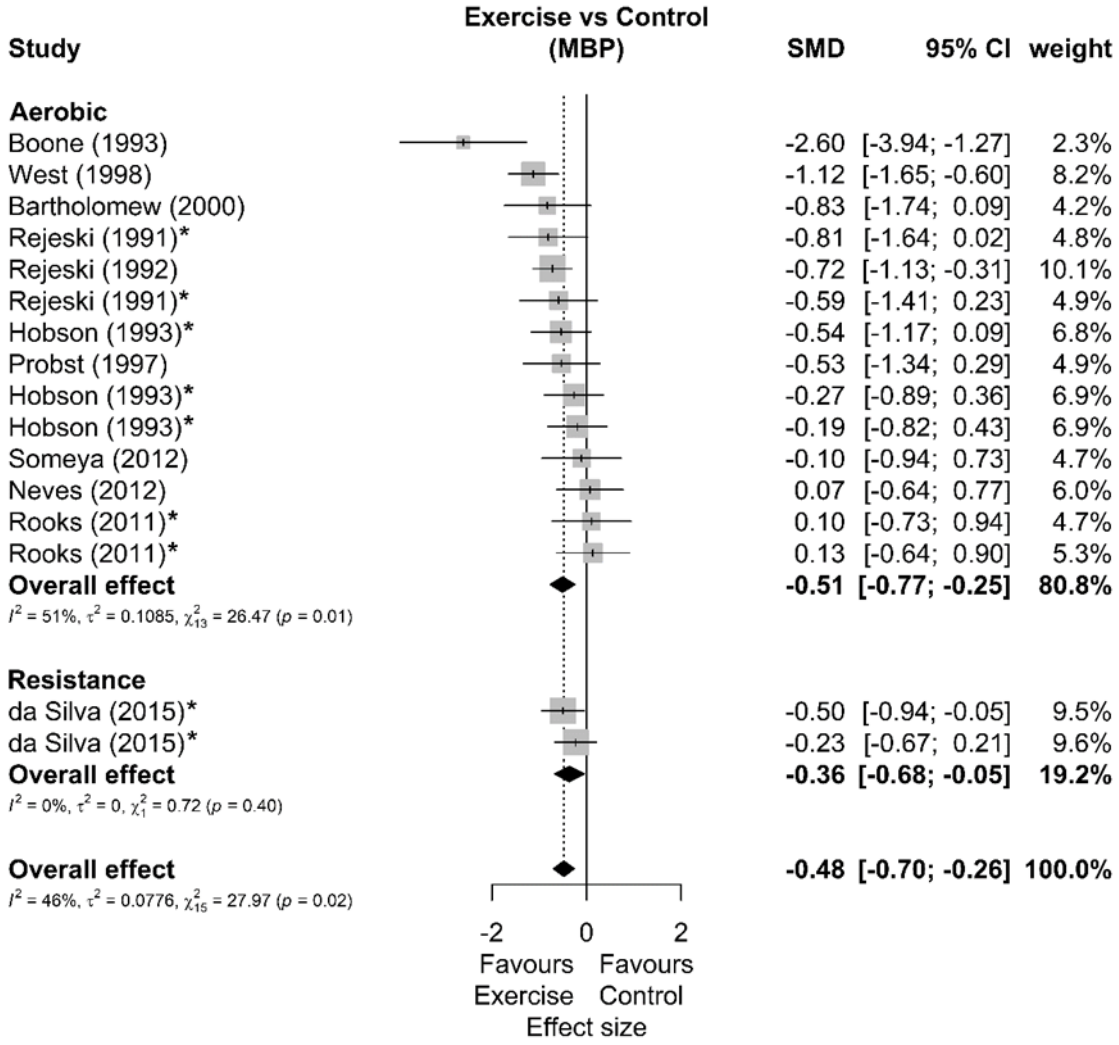

Figure 4 – *Mean blood pressure reactivity forest plot. SMD: standardized mean difference; MBP: mean blood pressure; CI: credible interval; *: studies with multiple comparisons.*

Sensitivity analyzes showed that 4 studies [26,27,34,44] can be outliers and/or influential points in DBP and 1 study [26] in SBP and MBP reactivity. New analysis disregarding these studies showed a DBP effect size of -0.30 [-0.43; -0.17], a SBP effect size of -0.34 [-0.45; -0.123] and a MBP effect size of -0.44 [-0.62; -0.27]. The BP reactivity effect size distribution and possible outliers can be visualized in *figure 5*. Subgroup sensitivity analyzes were performed in SBP and DBP, but none of these analyses reported significant differences between subgroups, whether it's splitted by: study design (SBP p: 0.73; DBP p: 0.30), participants sex (SBP p: 0.25; DBP p: 0.09), exercise mode (SBP p: 0.22; DBP p: 0.67), stress type (SBP p: 0.74; DBP p: 0.19) or number of stressors (SBP p: 0.94; DBP p: 0.23). The summary of these analyzes can be seen in S*upplement table 2*.

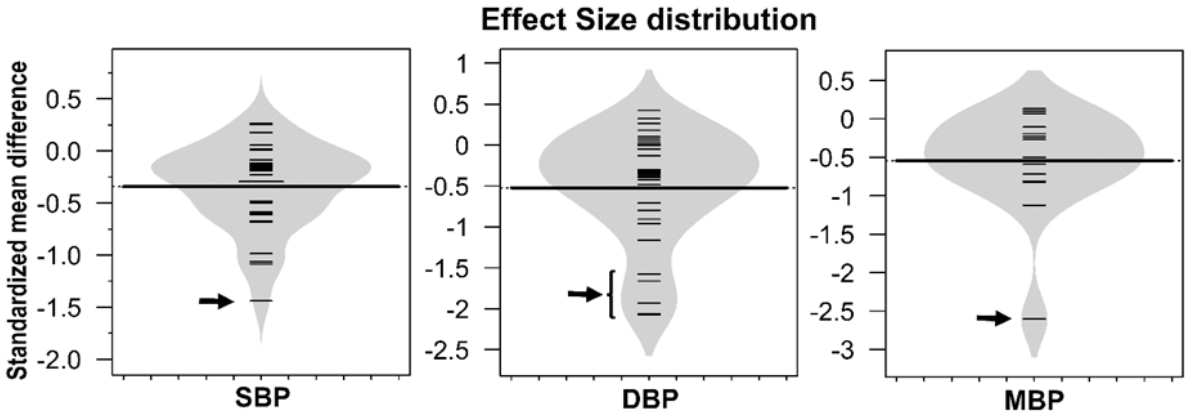

Figure 5 – *Beans plot with effect size distribution. Each small line represents a study effect size. The largest line of each Bean represents the average effect of the variable. Bean's shape represents the distribution of effect sizes. Arrows identify possible outliers. SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure.*

RISK OF BIAS ASSESSMENT

In general, studies present a low to moderate risk of bias in all domains (*Figure 6)*. Just one study mentions the previous existence of protocols or clinical study records, making it difficult to analyze bias related to selection of reported results. None of the studies reported conflicts of interest or participants were blinded to interventions, what is expected in physical exercise interventions and does not seem to be a major problem in this type of intervention [49].

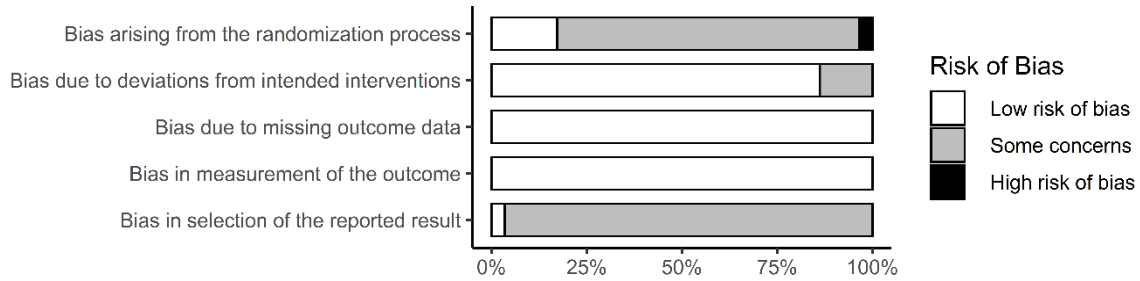

Figure 6 – *Risk of bias summary (k = 28).*

PUBLICATION BIAS ASSESSMENT

The publication bias tests showed no asymmetries in the funnel plot for SBP (Egger regression p = 0.575; Begg's test p = 0.697), DBP (Egger regression p = 0.450; Begg's test p =0.321) or MBP reactivity (Egger regression p = 0.733; Begg's test p = 0.528). However, six omitted results are expected by trim and fill funnel plots only in SBP (*figure 7*).

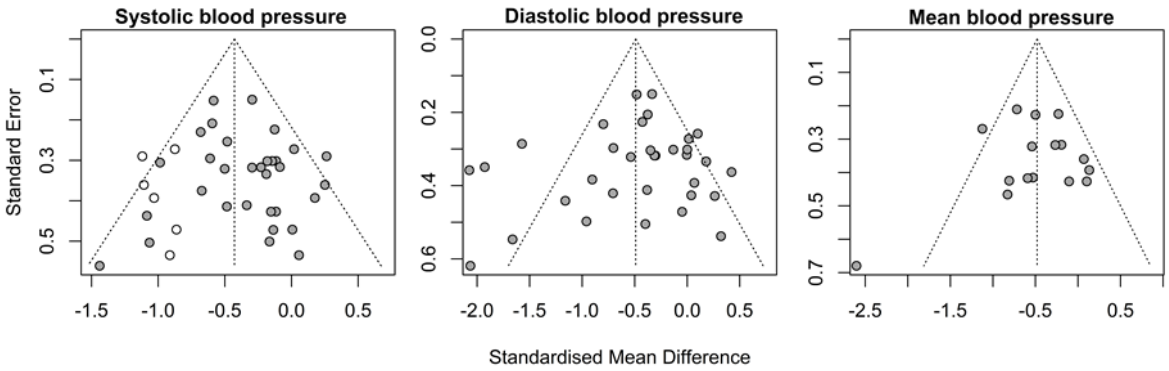

Figure 7 – *Publication bias representation by trim and fill funnel plots. White circles represent possible omitted studies.*

DISCUSSION

Our main results were that 61% (17 out of 28) of the included studies showed attenuated BP peaks (either in SBP, DPB and/or MBP) after acute exercise and none showed deleterious BP results from the exercise. The metanalytic results suggest that acute exercise attenuates BP reactivity to stress. This effect occurred mutually in SBP (Effect size = -0.35 [-0.46; -0.23]), DBP (Effect size = -0.49 [-0.68; -0.30]) and MBP (Effect size = -0.48 [-0.70;-0.26]) in magnitudes similar to previous meta-analyze about the effects of acute aerobic exercise (SBP Effect size = 0.38; DBP Effect size = 0.40) [12]. Besides that, only 22% of the studies included non-aerobic exercises which makes the results for these types of exercise difficult to generalize. Lastly, there is a scarcity of studies with hypertensive individuals (11%) and with a population over 40 years old (11%).

In this sense, we reaffirm the need for further studies with high cardiovascular risk patients, like hypertensive ones, since these responses contribute to the construction of the clinical picture of these patients and may indicate an increase in left ventricular mass [9], augmented carotid atherosclerosis [50], increased risk of cardiovascular mortality [51], development of hypertension [11], and an increased risk of developing several cardiovascular diseases [2,4]. We also extend this need for studies with the elderly, who, in addition to having the aforementioned advantages for having a high incidence of cardiovascular diseases [52], seem to have very promising responses when compared to younger people [53].

We also emphasize that, in addition to expanding and confirming favorable responses to aerobic exercise [12], the present study is, as far as we know, the first to demonstrate favorable meta-analytic effects of resistance exercise in SBP, DBP and MBP reactivity. It is worth mentioning that these results are anchored in a smaller volume of evidence, and should

be interpreted with caution, but it provides an optimistic direction for future studies with this exercise mode. But despite this, resistance exercise has shown favorable results for both physical [36] and mental stress [47] at intensity between 40-70% of one repetition maximum, but with null results post eccentric exercise at 120% of one repetition maximum. In addition, longer sessions (50min versus 30min) seem to have greater results [47]. Finally, combined aerobic and resistance exercises also shows positive results in SBP and DBP [30].

Regarding intervention characteristics, studies that compare different exercise loads showed mixed results. As an example, three studies evaluated different exercise intensity and one was favorable to higher intensities [20], another obtained a very discreet advantage at greater intensities [42], and the latter found no differences between groups that trained at 50 or 80% of VO_{2max} [35]. Concerning exercise session duration, a study shows favorable effects of longer session [47], and the others found no differences [27,41]. Finally, a study compared continuous aerobic exercise of moderate intensity with interval exercise of high intensity and also found no significant differences between the interventions [45]. Thus, evidence regarding the characteristics of exercise load control is still inconclusive.

As for the types of stressors, several were used by the studies included in the present study. From classically standardized and widely used protocols such as the Cold pressor test [54] to less restricted protocols but with greater ecological validity as studding situation [21]. In this sense, we believe that a convergence of these characteristics is necessary, to combine sufficient standardization of methods with greater continuity with the stress experienced in daily life [5]. Thus, studies with multiple stressors such as the Trier Social Stress Test (that includes public speaking with simulated job interview and arithmetic task) and the Maastricht Acute Stress Test (that includes cold pressure thermal stress, negative feedback and arithmetic task) seem to be good alternatives for future studies [5]. But despite their differences in methodology, the different types of stressors seem to have similar BP responses [5].

Like the types of stressors, their mechanisms of action are also diverse. So, when a stressful situation is imposed, it generates a response that includes diverse mechanisms [1–3], such as: neural-network (specially salience, executive control, and default mode networks) [55,56], autonomic system [57,58], catecholamines [3,59], cortisol [60,61], and opioids/β endorphin [62,63]. So, the isolated and interaction [64] effects of these mechanisms may explain the BP reactivity to stress [3,65]. Exercise, in turn, seems to mitigate stress reactivity by reducing vascular resistance [34], norepinephrine [66] and hypothalamic pituitary-adrenal

axis responses [67], in addition to causing increased β2-mediated vasodilation [66] and levels of endorphins [68]. Finally, there are also psychosocial effects of exercise such as improved self-efficacy and distraction from negative feelings [69].

It should be emphasized that the present systematic review has some limitations, such as the multiplicity of stress tests and exercise interventions, which makes difficult to fully understand and generalize the results. Besides that, laboratorial stress tests of short duration may not translate their results into conditions with extended stressors. Lastly, these results are mostly in healthy and young populations and therefore cannot be easily generalized to populations with different health conditions. Thus, in future studies we encourage the research of stressors similar to everyday life, involving different situations, sensations, emotions, and specially extended stressors like those found in sports, social fragility, and scholar/work environment. In these sense, we highlight a study [21], which despite achieving null results, has an interesting stressor approach with great ecological validity (40 minutes studying with undergraduate students). Finally, we also encourage studies that allow a better understanding of the characteristics of exercise load control (e.g. intensity, volume), and in older populations with different morbidities, that can help to improve individual intervention strategies.

CONCLUSION

In summary, acute physical exercise lowers SBP, DBP and MBP reactivity to stressor tests. So, physical exercise is an effective strategy to reduce hypertensive peaks under stressful situations in adults. However, given the small magnitude of effects found, the clinical relevance of this result must be interpreted with caution. So, more studies are needed to verify the magnitude of the reduction in stress responsiveness that, in the long term, would bring important clinical responses.

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SUPPLEMENTS

Supplement table1 - *Categorized search terms.*

Category	Terms
Exercise	Exercise; Exercise Therapy; Physical activity; Physical training; Aerobic; Cycling; Cycle ergometer; Cyclergometer; Cycle-ergometer; Hand grip; Hand-grip; Handgrip; Walking; Walk; Weight training; Weight-training; Weight exercise; Weight-exercise; Resistance exercise; Resistance training; Tai chi; Tai-chi; Isometric; High intensity; Moderate intensity; Low intensity; Combined training; Swimming; Swim; Running; Run; Strength; Pilates; Combined exercise; Concurrent training; Concurrent exercise; Yoga; Ioga; Hiit; Hit; Siit; Sit; Bicycle; Treadmill.
Stress test	Reactivity; Cold pressor; Stroop; Stress test; Psychosocial; Psychosocial test; Psychosocial stress; Psychosocial task; Math; Arithmetic; Arithmetic test; Arithmetic task; Stress task; Math task; Speech task; Speech.
Blood pressure	Arterial pressure; Blood pressure; Diastolic; Systolic.

Supplement table 2 – *Summary of sensibility analysis for blood pressure responsiveness.*

Subgroup variables	Effect size					Subgroup differences p	Heterogeneity		
	SMD	95% CI	Weight (%)	k	m		i² (%)	τ²	Q
SBP									
Exercise mode									
Yoga	0.15	[-0.33; 0.64]	4.9	2	2		0	0.0000	0.52
Aerobic	-0.37	[-0.50; -0.24]	76.9	17	25		15	0.0118	28.37
Combined	-0.30	[-0.92; 0.33]	3.0	1	1	0.22	-	-	-
Resistance	-0.40	[-0.66; -0.13]	15.3	3	4		24	0.000	3.92
Overall	-0.35	[-0.46; -0.23]	100	23	32		17	0.0145	37.33
Study design									
RCT	-0.39	[-0.67; -0.11]	19.2	3	6		37	0.0291	7.9
Cross over	-0.34	[-0.46; -0.21]	80.8	19	26	0.73	15	0.0111	29.34
Overall	-0.35	[-0.46; -0.23]	100	22	32		17	0.0145	37.33
Sex									
Men	-0.35	[-0.52; -0.17]	36.7	9	13		0	0.0000	11.39
Women	-0.36	[-0.59; -0.13]	21.2	4	8		0	0.0000	6.73
Both	-0.28	[-0.49; -0.07]	37.5	7	8	0.25	44	0.0289	12.42
Undefined	-0.85	[-1.37; -0.34]	4.6	2	3		32	0.0000	2.95
Overall	-0.35	[-0.46; -0.23]	100	22	32		17	0.0145	37.33
Stressor type									
Mental	-0.31	[-0.47; -0.14]	56.3	11	16		31	0.0262	21.68
Physical	-0.37	[-0.58; -0.15]	24.7	5	8	0.74	0	0.0000	6.82
Both	-0.42	[-0.68; -0.17]	19.0	6	8		16	0.0053	8.34
Overall	-0.35	[-0.46; -0.23]	100	22	32		17	0.0145	37.33
Number of stressors									
Multiple	-0.35	[-0.60; -0.11]	28.4	8	10		38	0.0452	14.45
Unique	-0.34	[-0.47; -0.22]	71.6	14	22	0.94	8	0.0029	22.77
Overall	-0.35	[-0.46; -0.23]	100	22	32		17	0.0145	37.33
DBP									
Exercise mode									
Yoga	-0.77	[-1.27; -0.27]	5.5	2	2		0	0.0000	0.2
Aerobic	-0.48	[-0.71; -0.24]	77.6	18	26		74	0.2440	96.83*
Combined	-0.30	[-0.93; 0.32]	3.2	1	1	0.67	-	-	-
Resistance	-0.50	[-0.86; -0.14]	13.6	3	4		57	0.0558	7.01
Overall	-0.49	[-0.68; -0.30]	100	24	33		70	0.1979	106.09*
Study design									
RCT	-0.79	[-1.45; -0.12]	19.2	3	6		88	0.5855	40.55*
Cross over	-0.42	[-0.60; -0.24]	80.8	20	27	0.30	58	0.1130	62.08*
Overall	-0.49	[-0.68; -0.30]	100	23	33		70	0.1979	106.09*
Sex									
Men	-0.49	[-0.85; -0.12]	38.4	9	13		77	0.3221	51.37*
Women	-0.35	[-0.65; -0.06]	23.1	4	8		42	0.0551	11.99
Both	-0.42	[-0.72; -0.12]	31.8	8	9	0.09	74	0.1360	31.35*
Undefined	-1.16	[-1.72; -0.59]	6.7	2	3		39	0.0217	3.29
Overall	-0.49	[-0.68; -0.30]	100	23	33		70	0.1979	106.09*
Stressor type									
Mental	-0.30	[-0.48; -0.12]	53.8	12	17		44	0.0495	28.44*
Physical	-0.56	[-0.82; -0.29]	24.5	5	8	0.19	39	0.0413	11.47
Both	-0.72	[-1.38; -0.05]	21.6	6	8		86	0.7464	48.32*
Overall	-0.49	[-0.68; -0.30]	100	23	33		70	0.1979	106.09*
Number of stressors									
Multiple	-0.69	[-1.18; -0.20]	29.0	8	10		83	0.4898	53.54*
Unique	-0.37	[-0.54; -0.20]	71.0	15	23	0.23	47	0.0672	41.84*
Overall	-0.49	[-0.68; -0.30]	100	23	33		70	0.1979	106.09*

*Include physical stressor: studies that used only physical stressors or in conjunction with mental stressors; SBP: systolic blood pressure; DBP: diastolic blood pressure; SMD: effect size by standardized mean differences; CI: credible interval; k: number of studies; m: number of comparisons; *: p<0.05.*

PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	89
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	90
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	91
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	91
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	91-92
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	92
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	92, 108
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	91-92
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	92
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	91-93
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	92
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	93
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	93
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis.	93
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	93
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	93
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	93
	13e	Describe any methods used to explore possible causes of heterogeneity among study results.	93
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	93

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	93
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	92
	16b	Cite studies that met many but not all inclusion criteria ('near-misses') and explain why they were excluded.	94
Study characteristics	17	Cite each included study and present its characteristics.	95-96
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	100
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	96-98
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	100-101
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	97-99
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	97-99
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	99, 109
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	100-101
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	101
	23b	Discuss any limitations of the evidence included in the review.	103
	23c	Discuss any limitations of the review processes used.	103
	23d	Discuss implications of the results for practice, policy, and future research.	103
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	91
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	91
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	-
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Aguardando versão final
Competing interests	26	Declare any competing interests of review authors.	Aguardando versão final
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Aguardando versão final

ESTUDO 6

STRESS-INDUCED BLOOD PRESSURE AFTER EXERCISE TRAINING: A SYSTEMATIC REVIEW WITH META-ANALYSIS.

Igor M. Mariano, Ana Luiza Amaral, Paula A. B. Ribeiro, Guilherme M. Puga

Status: não publicado.

ABSTRACT

Background: Exercise and acute stress tests are important tools for risk stratification in the clinical routine. Blood pressure (BP) reactivity to stress is related to future cardiovascular events and hypertension development, so tolerance to acute stressors is important to better manage cardiovascular risks. Exercise training is among the strategies that have been tested to improve tolerance to acute stressor, however its efficacy is poorly explored. **Methods**: This is a systematic review with meta-analysis that examined the effect of exercise training (at least 4 weeks) on BP peaks/variation in responses to laboratory stressor tasks in adults. The searches were performed in 4 digital databases (PUBMED, LILACS, EMBASE and PsycInfo) and 20 studies and 2 conference abstracts were included, totaling 945 individuals (k = 12 and n = 516, in the meta-analysis stage). **Results**: Favorable results (Random effects) for exercise training were found, with attenuated hypertensive peaks in systolic (mean effect size = -0.47 [-0.69; -0.24], representing average reductions of 2.6 ± 3.5 mmHg) and diastolic BP (mean effect size = -0.35 [-0.58; -0.12], representing average reductions of 4.5 ± 3.8 mmHg). **Conclusions**: Exercise training lowers stress related systolic and diastolic blood pressure reactivity. So, it can improve the ability to better respond to stressful situations, mitigating hypertensive peaks.

Key Words: Aerobic Exercise; Resistance Exercise; Hypertension; Cardiovascular; Stress; Reactivity.

INTRODUCTION

Modern life provides several stressful situations in which homeostasis is actually or perceived to be challenge [1]. These episodes induce responses from different mechanisms such as catecholaminergic, neural networks and autonomous systems [1–3]. These responses generate changes in clinically important outcomes, of which we highlight the blood pressure (BP) reactivity. So, assessing hypertensive peaks in response to controlled stressors through simple laboratory tests can indicate, independently of resting BP, the development of future cardiovascular events [4,5], hypertension [6,7] and decreased telomere length [4]. This is accomplished through different protocols that involve physical stressors (i.e. physiological or environmental), mental stressors (emotional or cognitive) or a mix of both [5]. In this way, one of BP's control strategies is to perform recurrent physical exercises [8]. However, the influence of this strategy to control BP reactivity to stressful situations is still poorly understood.

Previous meta-analysis about the acute effect of aerobic exercise on BP reactivity [9] found protective effects, with attenuated hypertensive peaks. Moreover, a systematic review [3] assessed the effects of exercise training and aerobic physical fitness on several cardiovascular markers and found blunted BP reactivity results, reiterating the importance of the exercises to mitigate hypertensive peaks. However, these results are not consistent. A meta-regression found no improvement in BP reactivity associated with aerobic physical fitness [10]. Besides that, the meta-analytic effects of exercise training on BP reactivity to external stressors have not yet been described. Thus, the objective of the present study was to investigate the effects of exercise training on BP peaks/variation in response to laboratorial stress tasks in adults. Our hypothesis is that exercise training, attenuates BP reactivity to stress, reducing hypertensive peaks and cardiovascular risk of these individuals.

METHODS

This systematic review with meta-analysis was registered on the “PROSPERO” platform (CRD42020195700), had its protocol published on the “protocols.io” platform [11] and followed PRISMA guidelines [12,13].

ELIGIBILITY CRITERIA

Studies with the following characteristics were eligible: clinical trials in English, Portuguese, or Spanish with no design limitations; only studies in human adults of both sexes; the intervention was physical exercise training for at least 4 weeks and as control a group

without exercise; the outcome of interest was BP reactivity (peak BP or BP variation from baseline) during laboratory stressor after exercise training; with no limit for publication dates.

The exclusion criteria are: literature reviews, meta-analysis, letters to the editor, observational studies, animal studies, population under 18 years old, studies written in other languages not described above, studies whose exercise intervention was relaxation, stretching, breathing exercises or cardiovascular rehabilitation after serious cardiovascular events, and studies that do not measure BP during the stress tests.

SEARCH STRATEGY

The searches were realized in digital databases (PUBMED, LILACS, EMBASE and PsycInfo), in the references of the main articles, and through manual search until March 17th, 2021. When necessary, we contacted the authors. The search was divided into 3 categories of terms: exercise, blood pressure and stress tests. Within each category, the terms were separated by union operators (i.e. "OR") and the categories were separated by parentheses and intersection operators (i.e. "AND"). All terms of the search are shown in the *Supplement table 1* and the flow diagram is show in *figure 1*.

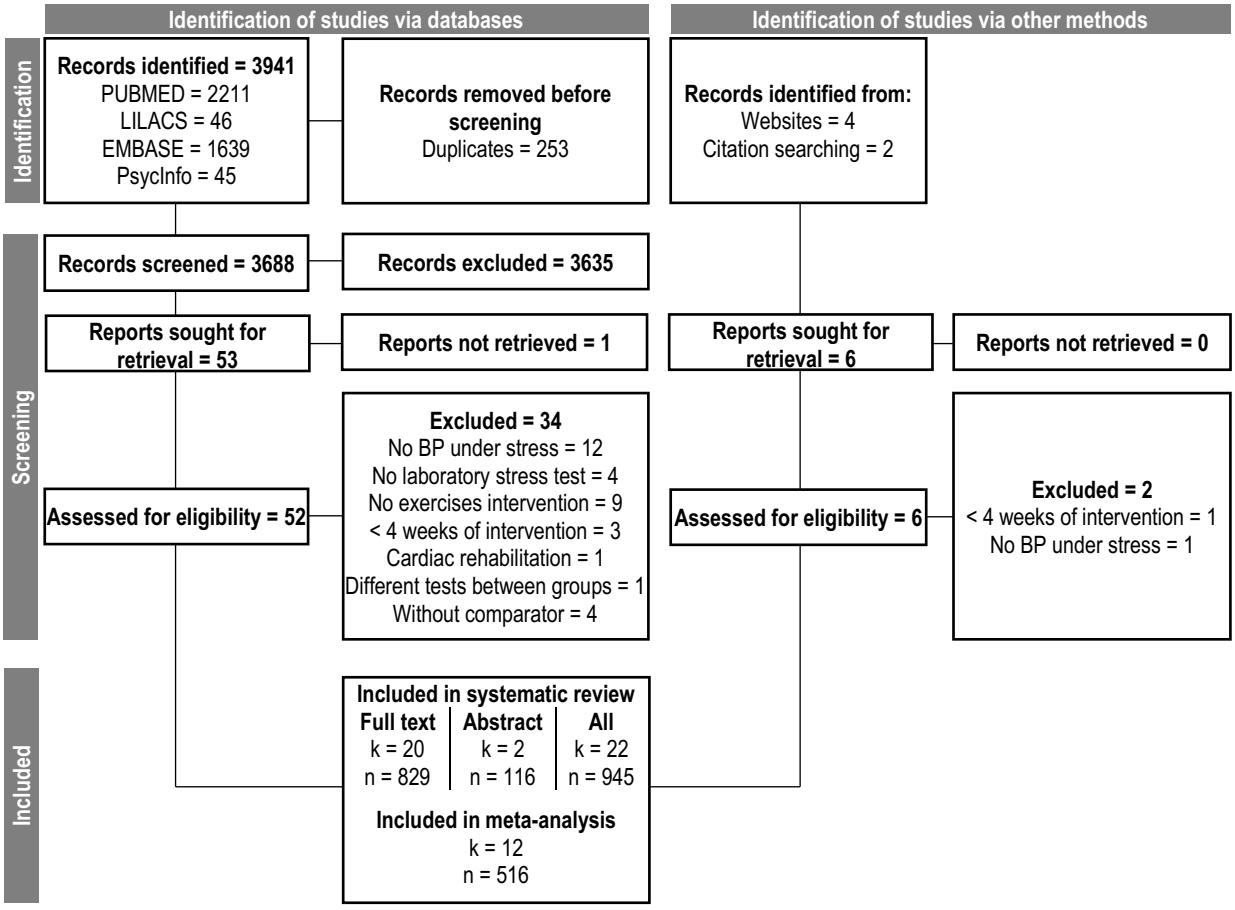

Figure 1 – *Flow diagram. k: number of studies, n: pooled sample size, BP: Blood pressure.*

SCREENING AND DATA EXTRACTION PROCESS

During the entire process (screening, data extraction and risk of bias assessment), the studies were evaluated in duplicate by independent reviewers (IMM and ALA). After checking the reviewers' responses, the disagreements were resolved by consensus or by a third reviewer when necessary (GP). After the title and abstract screening phase, one of the reviewers standardized alphanumeric codes for all studies that would be part of the subsequent analyzes. Thus, each reviewer independently filled an electronic datasheet detailing the characteristics of the studies, and the data was compared to assess agreement and identify extraction errors. This datasheet included: general description (unique identification code, author, publication year, language, and study design), participants description (sexes and respective sample sizes, participants health and fitness status, age, hypertension status, other comorbidities, and other relevant characteristics), exercise description (intensity, volume, frequency, exercise mode, and other relevant characteristics); stressor description (stressor test, blood pressure measurement device/technique, and other relevant characteristics), and outcome measures (SBP and DBP reactivity) for intervention and comparator groups (sample sizes, centrality and dispersion measures, and other relevant characteristics). In studies in which the data are presented only in graphs or figures without clear numerical representation, the data was extracted by the web-based software “WebPlotDigitizer”. When there was not enough data for quantitative analysis, the authors were contacted requesting these data.

STATISTICAL ANALYSIS

The data was evaluated using the “R” programming language through the supplements "meta" [14] and "metafor" [15]. They were analyzed based on standardized mean differences (SMD). In studies that presented multiple stress tests, we used the average test results with the respective pooled dispersion measure. Kendall's tau and I^2 were calculated as heterogeneity measures. The summary meta-analysis values were carried out from a random-effects approach by Hunter Smith method. The random-effects model was defined due to the inherent heterogeneity of the characteristics of the studies, such as exercises of different modalities and varied stress tests. As there were not enough studies of different modalities that were not aerobic, the network analysis provided for in the protocol was not performed [11].

The sensitivity analysis was done through the search for outliers using the “externally standardized residuals” method, the search for influential points using the difference in fits, covariance ratio and Cook’s distance methods, and subgroup analysis (splitting by type of stressor, number of stressors, and existence of hypertension). The risk of bias assessment was

carried out at the level of studies using the tool “Risk of Bias 2.0” from the Cochrane collaboration [16] and its graphical visualization by the “R” supplement "robvis" [17]. Publication bias analysis was carried out through a funnel plot and asymmetry hypothesis tests (Rosenthal fail-safe n, Egger’s regression and Beggs test). The agreement between reviewers was estimated from Cohen's kappa in both full text screening ($\kappa = 0.806$; $p < 0.001$) and risk of bias assessment stages ($\kappa = 0.885$; $p < 0.001$).

RESULTS

QUALITATIVE RESULTS

The main characteristics of the studies (20 studies and 2 conference abstracts) are shown in *table 1*. Only randomized clinical trials were found, and the most frequent laboratory stress tests used is the Arithmetic test (7 studies) followed by the Cold pressor test (5 studies). The duration of exercise interventions varied between 6 and 52 weeks (average of 18 weeks). On average, the exercise sessions had 50 minutes, intensities between 60-80% (moderate to high) of an individual parameter (e.g. maximum oxygen consumption, peak heart rate), and frequency between 3 and 4 times a week. Besides that, the studies included women (n = 310), men (n = 505), normotensive (n = 476) and hypertensives (n = 237), in addition to 14 in whom the proportion of sexes are not clear and 116 individuals in whom the proportion of hypertensive patients are not clear.

Table 1 – *Studies characteristics.*

Study	Population	Stress test	Exercise	Reactivity results
Included in systematic review and meta-analysis				
[18]	HT, 24 women + 31 men, 48 years, sedentary, overweight	Public speaking + Cold pressor + Anger interview + Mirror tracing	Aerobic (Walk or cycle), 26 weeks, 03-04 times weekly, for 65 minutes, at 70-85% VO_{2max}	↓SBP ↓DBP
[19]	NT, 22 men, 24 years, sedentary	Cold pressor + Memory search + Tone avoidance	Aerobic (Run or aerobics class), 7 weeks, 4 times weekly, for 90 minutes, at Moderate (2x) and High (2x) intensities	↔SBP ↔DBP
[20]	60 NT+ 25 HT, women, 63 years, sedentary, family caregivers	Public speaking	Aerobic (Brisk walk), 52 weeks, 4 times weekly, for 30-40 minutes, at 60-75% $HR_{reserve}$	↓SBP ↓DBP
[21]	NT+HT, 8 women + 17 men, 67 years, silent myocardial Ischemia	Anger-recall task + Arithmetic + Role play	Aerobic (Walk), 26 weeks, 3 times weekly, for 40 minutes, at 70% $HR_{reserve}$	↔SBP ↓DBP
[22]	HT, 23 men, 41 years	Stroop color	Aerobic (Walk or run), 12 weeks, 3 times weekly, for 45 minutes, at 40-50% (LI) or 70-80% (MO) VO_{2max}	LI: ↓SBP e ↓DBP. MO: ↔SBP e ↓DBP
[23]	NT, 14 women + 16 men, 22 years, sedentary	Arithmetic	Aerobic (Run, cycle, swim, rowing, or stair climbing) or Resistance exercises, 6 weeks, 03-05 times weekly, for 40-45 minutes, at 70-85% HR_{max} or 8-12 repetitions	Aerobic and resistance groups: ↓SBP e ↔DBP
[24]	NT, 40 women + 43 men, 48 years, sedentary	Arithmetic	Aerobic (Brisk walk or run), 26 weeks, 5 times weekly, for 47-54 minutes, at 65-77% HR_{peak}	↔SBP ↔DBP
[25]	NT, 34 men, 25 years, sedentary	Stroop color	Aerobic (Cycle), 12 weeks, 3 times weekly, for 30 minutes, at 80-90% HR_{max}	↔SBP ↔DBP
[26]	HT, 11 women + 13 men, 64 years	Arithmetic + Cold pressor + Hand grip	Hand grip, 10 weeks, 3 times weekly, for 12 minutes (4x2'/1'), at 30% Maximum voluntary isometric contraction	Arithmetic and hand grip: ↓SBP ↔DBP. Cold: ↔SBP ↔DBP
[27]	HT, 16 women + 14 men, 42 years, sedentary	Arithmetic	Aerobic (Cycle), 8 weeks, 3 times weekly, for 30 minutes, at variable intensity	↔SBP ↔DBP
[28]	HT, 11 women + 44 men	Hand grip	Yoga, 12 weeks, 3 times weekly, for 45 min	↑DBP
[29]	14 women, 36 men	Valsalva + Hand grip + Tilt test	Aerobic (Walk/run), 12 weeks, 3 times weekly, for 40 min, at 60-75% HR_{max}	↓SBP
Included only in systematic review				
[30]	NT, 37 men, 42 years	Arithmetic	12 weeks of Aerobic (Walk or run, 3 times weekly, for 50 minutes, at 70% VO_{2max}) or Resistance (2 times weekly, 20 minutes of flexibility + 30 minutes of resistance exercise circuit)	↓SBP ↓DBP
[31]	NT, 46 pre- and post-menopausal women, 50 years	Public speaking + Cold pressor	12 weeks of Aerobic (Walk or run, 3 times weekly, for 50 minutes, at 70% VO_{2max}) or Resistance (2 times weekly, 20 minutes of flexibility + 30 minutes of resistance exercise circuit)	Cold: Postmenopausal ↔SBP ↓DBP, Premenopausal ↔SBP ↔DBP. Speech: both ↔SBP ↔DBP
[32]	HT, 14 patients	Valsalva + Hand grip	Yoga, 6 weeks, 6 times weekly, for 30 min	Hand grip: ↓SBP ↔DBP, Valsalva: ↓SBP ↓DBP
[33]	3 women + 38 men, Firefighters	Video-based Strategy and Tactics Drill	Aerobic (Rowing), 16 weeks, 4 times weekly, for 40 min, at variable intensity	↓MBP
[34]	16 NT+ 11 HT, men, 41 years	Attention task	12 weeks of Aerobic (Walk, run or stair climbing, 3 times weekly, for 50 minutes, at 70% VO_{2max}) or Resistance (2 times weekly,	↔SBP ↓DBP

			20 minutes of flexibility + 30 minutes of resistance exercise circuit)	
[35]	NT, 36 men, 44 years	Arithmetic	12 weeks of Aerobic (Walk, run or stair climbing, 3 times weekly, for 50 minutes, at 70% VO_{2max}) or Resistance (2 times weekly, 20 minutes of flexibility + 30 minutes of resistance exercise circuit)	Aerobic: ↓SBP ↓DBP. Control: ↔SBP ↓DBP
[36]	NT, 24 men, 33 years, sedentary	Cold pressor + Memory search + Tone avoidance	Aerobic (Run, jump, stair climbing, soccer or basketball), 32 weeks, self-selected frequency, for 120 min, at 70% HR_{max}	↔SBP ↔DBP
[37]	NT, 38 women + 50 men	Trier Social Stress Test	Aerobic, 3 times weekly, 26 weeks, 45-60 min, 75% HR_{peak}	↔SBP ↔DBP
[38]*	36 participants, chronic kidney disease	Hand grip	Aerobic (Cycle), 12 weeks, 3 times weekly, for 20-45 minutes, at 80% $HR_{reserve}$	↔BP
[39]*	80 participants, 18-50 years, healthy	Cold pressor	Yoga or Aerobic (Swim), 12 weeks	Cold: ↓SBP ↔DBP

*The age refers to the average. BP: blood pressure; SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure HR: heart rate; HT: hypertensives; NT: normotensives; LI: low intensity; MO: moderate intensity; * only abstracts presented in scientific events available.*

Regarding exercise mode, 18 studies referred to aerobic training, 2 to yoga training, 5 to resistance training and 1 to isometric handgrip training. However, 4 of the studies (published from 1988 to 1991) with aerobic exercises [30,31,34,35] had as a comparator group individuals that trained flexibility and resistance circuit exercises with volume, frequency and intensities smaller than the aerobic. Thus, they used an active comparator with exercise and therefore were disregarded in the meta-analysis. In addition, some studies [32,34–36] did not present enough data and therefore were also not included in the meta-analysis.

Considering the main results of the 20 studies, 9 found significative reductions in systolic (SBP), 9 in diastolic (DBP) and 1 in mean BP reactivity. The latter, being the only one to measure mean BP (MBP), was also not included in the meta-analysis. Only 1 study found worsening of DBP reactivity with Yoga intervention [28]. Based on qualitative analyzes, we did not identify exercise characteristics that distinguish studies with significant and non-significant responses. However, as for population, in the DBP reactivity, only two of the studies with favorable results did not include hypertensive patients. In addition to these, we found two abstracts presented in scientific events, which we have not identified related publications [38,39]. The most recent of these [38], reports finding no change in BP reactivity during the handgrip test after 12 weeks of cycling in patients with chronic kidney disease. The other [39] reported decreased reactivity of SBP but not DBP to the cold pressor test after 12 weeks of yoga compared to swimming.

META-ANALYSIS RESULTS

Among 12 studies included in the meta-analysis, three presented two possible comparisons with a control group without exercise according to the exercise intensity [22], exercise mode [23], and sex [24]. In addition, one study only shows results for SBP [29] and another only for DBP [28], resulting in 11 studies and 14 comparisons analyzed in each variable. Regarding the characteristics of the exercise, the duration, frequency, volume, and intensities are similar to the studies considered in the qualitative phase. The forest plots of SBP and DBP reactivity in relation to control are present in *figures 2 and 3,* respectively. We found favorable results to exercise in SBP (Effect size = -0.47 [-0.69; -0.24], representing average reductions of 2.6 ± 3.5 mmHg) and DBP (Effect size = -0.35 [-0.58; -0.12], representing average reductions of 4.5 ± 3.8 mmHg), demonstrating the capacity of exercise training to reduce BP variations caused by external stressors. Sensitivity analyzes showed that only one study [27] could be an outlier and an influential point just in DBP reactivity. An analysis of DBP disregarding this study showed an effect size of -0.27 and credible interval of -0.45 to -0.08. The discrepancy in the effect size of this study can be visualized in *figure 4*.

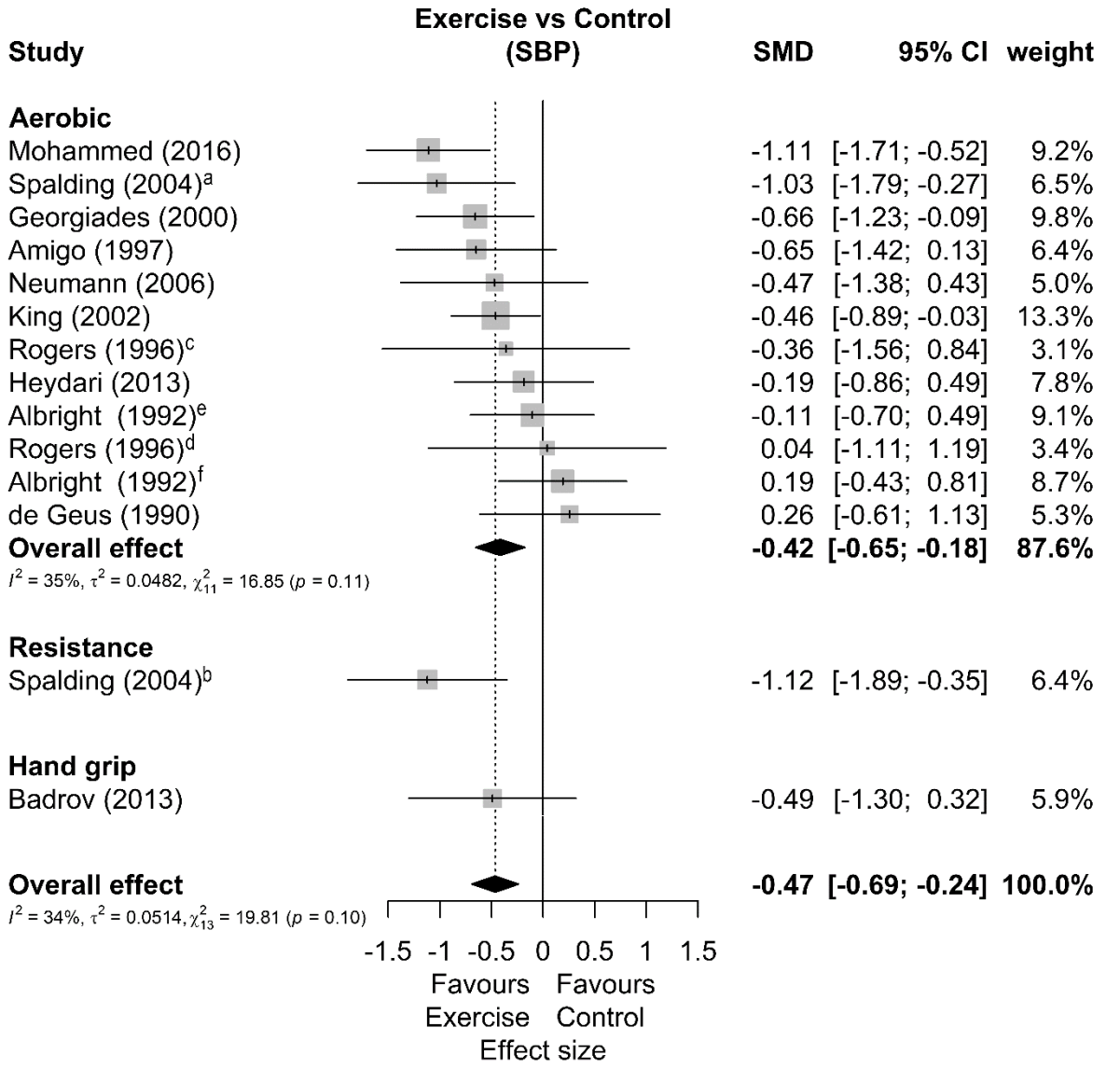

Figure 2 – *Systolic blood pressure reactivity forest plot. Studies with more than one comparison have a description of the considered comparison with the year of publication. SMD: standardized mean difference; SBP: systolic blood pressure; CI: credible interval; Superscript letters represent studies with multiple comparisons; [a]: aerobic exercise; [b]: resistance exercise; [c]: low intensity exercise; [d]: moderate intensity exercise; [e]: men; [f]: women.*

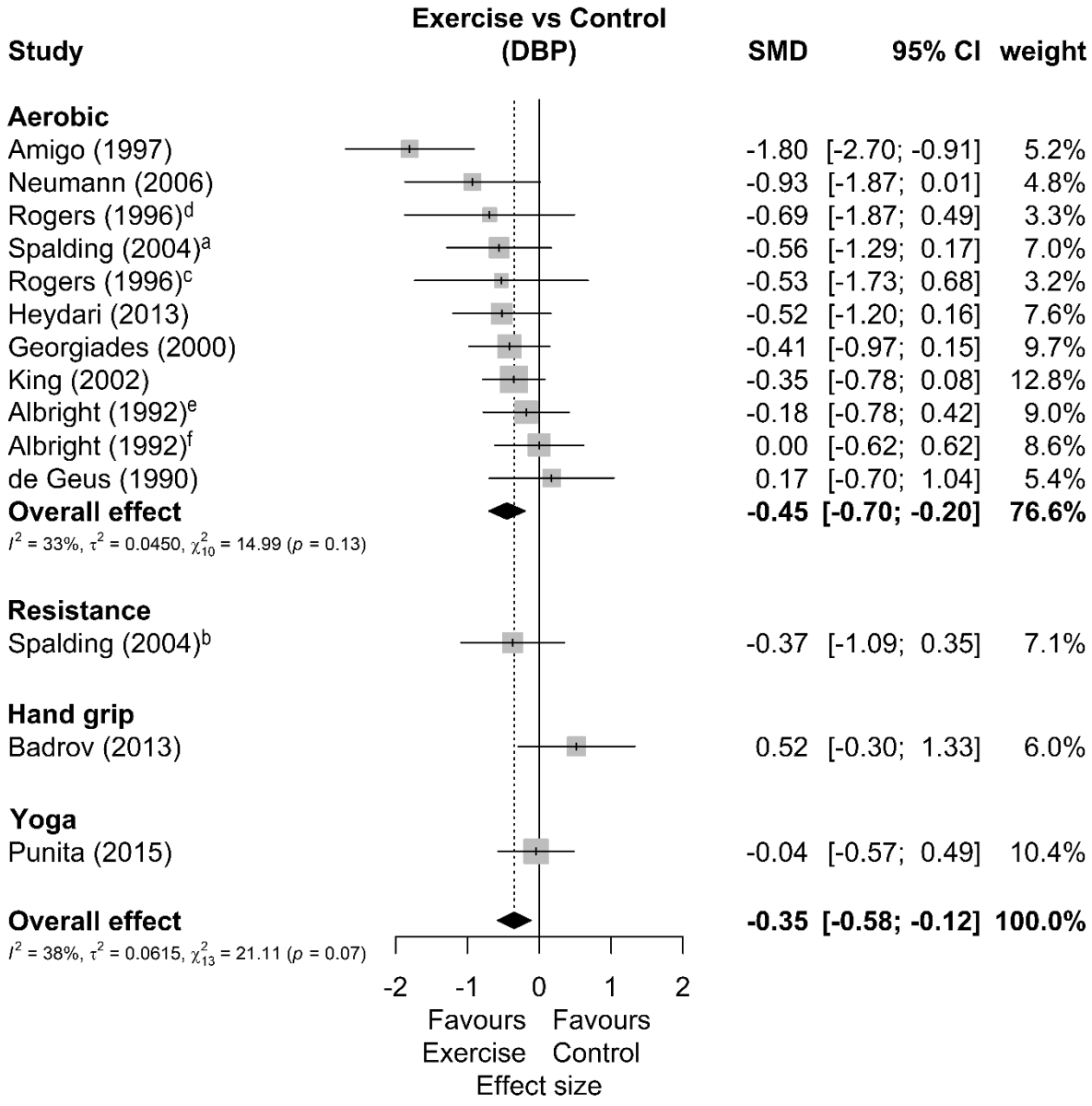

Figure 3 – *Diastolic blood pressure reactivity forest plot. Studies with more than one comparison have a description of the considered comparison with the year of publication. SMD: standardized mean difference; SBP: systolic blood pressure; CI: credible interval; Superscript letters represent studies with multiple comparisons; [a]: aerobic exercise; [b]: resistance exercise; [c]: low intensity exercise; [d]: moderate intensity exercise; [e]: men; [f]: women.*

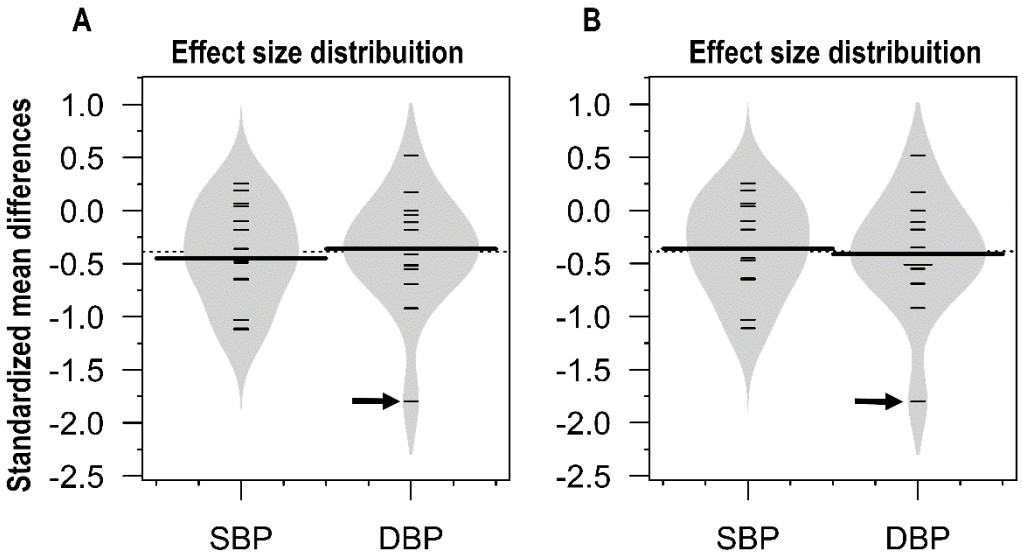

Figure 4 – *Beans plot with effect size distribution. Panel A: all studies included in metanalysis (k = 12). Panel B: only aerobic exercise studies (SBP k = 10; DBP k = 9). Each small line represents a study effect size. The largest line of each Bean represents the average effect of the variable, and the dotted line shows the general average. Bean's shape represents the distribution of effect sizes. The arrow indicates a possible outlier. SBP: systolic blood pressure; DBP: diastolic blood pressure.*

Other sensitivity analyzes were performed considering only studies with aerobic exercises, since these represented a large part of the sample. When separating the studies by type of stressors (only mental/psychological stressors against studies that included physical stressors), we did not find significant differences in the reactivity of SBP ($p = 0.39$) or DBP ($p = 0.34$). In addition, when separating the studies by number of stressors (unique or multiple stressors) we find no significant differences in SBP ($p = 0.31$) or DBP ($p = 0.70$) reactivity. Lastly, when separating studies by population (only normotensive, only hypertensive or both) we also found no significant differences in the reactivity of SBP ($p = 0.14$) or DBP ($p = 0.17$). The summary of these analyzes can be seen in S*upplement table 2*.

RISK OF BIAS ASSESSMENT

The graphical summary of the risk of bias assessment is shown in *Figure 5*. This analysis excludes studies that have only been presented at scientific events without publishing a full text [38,39]. The risk of bias associated with deviation from the intended interventions is mainly due to large sample losses during training. It is worth mentioning that none of the studies were participants blinded to interventions, as this is difficult to do with physical exercise interventions. In addition, just one study mention the previous existence of previous protocols,

clinical study records or analysis plans, which could prevent self-selection of analyzes and results. None of the studies reported conflicts of interest.

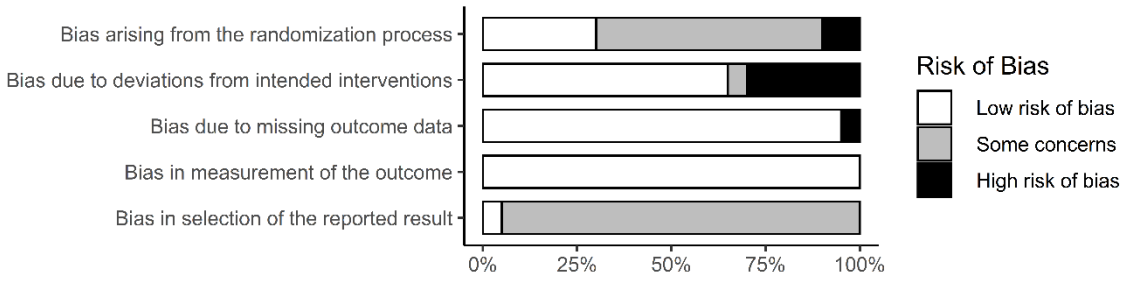

Figure 5 – *Risk of bias summary (k = 20).*

PUBLICATION BIAS ASSESSMENT

The publication bias tests showed no asymmetries in the funnel plot for SBP (Egger regression p = 0.744; Begg's test p = 0.411; Fail safe n = 101) or DBP reactivity (Egger regression p = 0.334; Begg's test p = 0.208; Fail safe n = 62). The funnel plots are presents in *figure 6*.

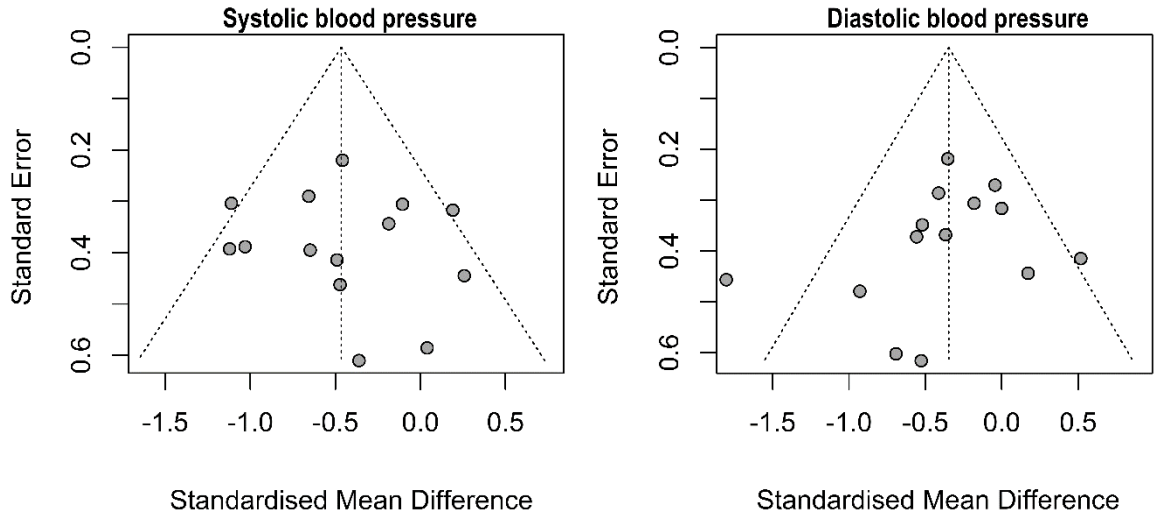

Fig. 6 – *Publication bias representation by funnel plots.*

DISCUSSION

Our main qualitative results were that most of the studies (64%) showed favorable BP responses (either in SBP, DPB and/or MBP) after exercise training, and the most frequent stressor test was the arithmetic task (7 studies). The quantitative analysis also suggests a moderate effect of exercise training attenuating BP reactivity to stress. This result occurred both in SBP (Effect size = 0.47 [-0.69;-0.24]) and DBP (Effect size = 0.35 [-0.58;-0.12]) and in magnitudes similar to previous meta-analysis about the effects of one session of aerobic

exercise (SBP Effect size = 0.38; DBP Effect size = 0.40) [9]. However, it is worth mentioning that the available data about non-aerobic activities are quite limited and, therefore, should be interpreted with caution.

Concerning the quality of the included studies, we emphasize that none of them has blinding participants regarding the interventions. However, this feature did not result in a high risk of bias in exercise training trials [40], especially if the important co-interventions were balanced between the groups, and there were no deviations from the intended interventions that would likely impact the result – which is in accordance with the algorithm proposed by the tool used [16]. Furthermore, a previous meta-analysis found no significant association between physical therapy treatment effects and adequate blinding [41]. Besides that, although they were described as randomized, they do not describe this process with sufficient level of detailing; and they do not present records of protocols, analysis plans or clinical study records, so that the evaluation of the selection of reported results bias was compromised. Thus, the studies included were generally of satisfactory quality, but with some concerns that should be polished in later studies.

Regarding studies that were not considered in the meta-analysis phase, we highlight that four had an active control group [30,31,34,35]. These studies had comparator groups that trained resistance circuit exercises with volume, frequency, and intensities smaller than the aerobic. Originally, these comparators were treated as controls, as it was considered that they would not cause significant cardiovascular changes [34]. Nevertheless, we believe that resistance exercise can cause significant cardiovascular changes [42], so we excluded these studies from the meta-analysis to control additional heterogeneity.

POSSIBLE MECHANISMS

When acute stress is inflicted, a complex physiological reaction is triggered that involves neural-network, physiological and endocrinological mechanisms [1–3]. So, increased secretion levels of adrenaline/noradrenaline from sympathoadrenal axis [1,43,44] and of cortisol from hypothalamic pituitary adrenal axis [45–47]**,** besides alterations in neural-network (such as salience network, default mode network, and executive control network, with the former predominating over the latter) [48,49] and autonomic system (with reduced vagal tone mediated by medullary mechanisms of the brain stem) [50–53] may explain the increase in BP levels under stressful situations [1,54]. It is worth mentioning that these mechanisms have interactions and that they act in an associated and not isolated way [54,55]. Physical exercise

training, in turn, can possibly decrease BP reactivity to stressful situations by attenuating adrenaline/noradrenaline [56], cortisol [57,58] and autonomic responses [59–61].

STRESSORS AND POPULATION CHARACTERISTICS

There are several assessment methods that involve physiological, environmental, emotional, cognitive or multiple stressors, and that may involve social-evaluative threat, uncontrollability and unpredictability [5]. Despite their differences in methodology and physiological mechanism of action, the different types of stressors seem to have similar BP responses [5]. As an example of the mechanisms of action to increase BP, a physical stressor (i.e. Cold pressor test) seems to act through arteriolar vasoconstriction [62], by sympathetic adreno-medullary axis activation but minimal hypothalamic-pituitary-adrenal axis stimulation [5]. A mental stressor (i.e. Stroop color and word test) in its turn, could cause an increase in heart rate and pulse pressure with no changes in the stroke volume, in vascular resistance nor did it affect central arterial wave reflection [63], showing less vascular protagonism.

Several population characteristics can influence BP reactivity. Older adults seem to be more responsive to stress than younger adults [64]. In addition, hypertensive individuals seem to have greater vascular and lower cardiac output responses associated with vascular and ventricular hypertrophies, respectively [63]. Men seem to have a more exacerbated reactivity than women [65,66], and the women climacteric phase seems not to influence these responses prior to exercise, being that post-menopausal women showed greater catecholamines reactivity after 12 weeks of aerobic exercises [31]. On the other hand, affective state [44], self-efficacy [67], familiarity with the tests, and the application moment of the tests after the exercise training could be confounding factors that would explain part of the improvements [9]. However, these information are not well described in most exercise training studies, which did not allow us to use it in the sensitivity analyzes of the present study.

CLINICAL IMPLICATIONS

Clinically, the high reactivity to acute stress may indicate the development of cardiovascular disease [3,4] and a higher risk of cardiovascular mortality [68]. In this sense, there are indications that cardiovascular responses to stress are better predictors of left ventricular mass [69] and the development of hypertension [6,70] then resting BP. These characteristics added to the indication that hyper-responsive individuals in laboratory tests experience more stress daily [71], suggest that these tests can be important markers of

cardiovascular responses to everyday stress and a good risk stratification tool, therefore needs to be better explored.

In its turn, exercise training reduces several risk factors [72], including the ability to reduce BP comparable to antihypertensive drugs [73], making it a protagonist in health interventions. In this way, based on the findings of the present systematic review, moderate to high-intensity aerobic exercises demonstrated to be potential strategies capable of reducing the BP reactivity (either SBP, DBP or both) in different populations (e.g. men and women, normotensive and hypertensive) and under different stressors types, even if this is not consistent across studies [19,24,25,27,28,36]. Besides that, both resistance [23] and isometric handgrip [26] training also showed promising SBP results (effects sizes of -1.12 and -0.49 respectively), but with limited evidence. Regarding DBP reactivity, non-aerobic modalities have not shown promising results. Thus, future studies may focus on non-aerobic interventions to provide more accurate recommendations regarding these.

LIMITATIONS AND FUTURE PERSPECTIVES

It is worth noting that the present study has some limitations, such as the wide variety of stress tests used, which makes it difficult to understand the patterns of response to each type of stress and exercise, in addition to increasing the heterogeneity across studies. Besides that, most of the included studies performed aerobic exercises, limiting the understanding of the results for other types of exercise. Finally, idiosyncratic features of laboratory stress tests that use stressors of short duration (i.e. a few minutes) and that may not have their results translated into situations in which stressors extend for longer.

Thus, as future perspectives, we encourage exploring the effects of non-aerobic exercise modalities, in addition to studies involving stressors with greater similarity to daily situations, involving different sensations (e.g. pain, cold, heat, tiredness, loss of control, pressure for performance, frustration, fear, anger), and even prolonged stressors such as those found in situations of social fragility, and in the work or competitive sporting environment. In this sense, a good example of a study included in this systematic review that has a good coupling between the proposed stress and the reality of the population studied is [33]. This study carried out with firefighters, used a video test that proposes risk situations in which they should make difficult decisions in a limited time, which fits into the stressful situations they will face.

CONCLUSIONS

In summary, exercise training lowers SBP and DBP reactivity to laboratorial stress tests. The available evidence suggests that physical exercise is a good strategy to control not only resting BP but also its levels under stress. In this way, we reinforce the importance of recommending aerobic exercise training, as it can improve the ability to better respond to stressful situations, mitigating hypertensive peaks. However, given the small magnitude of effects, the clinical relevance of this result must be interpreted with caution. So, new studies are needed to verify the clinical significance of different reduction magnitudes in stress responsiveness.

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SUPPLEMENTS

Supplement table 1 - *Categorized search terms.*

Exercise			Blood Pressure	Stress test
Exercise	Hand grip	Tai chi	Arterial pressure	Reactivity
Exercise Therapy	Hand-grip	Tai-chi	Blood pressure	Cold pressor
Physical activity	Handgrip	Isometric	Diastolic	Stroop
Physical training	Walking	Hiit	Systolic	Stress test
Aerobic	Walk	Hit		Psychosocial
Cycling	Weight training	Siit		Psychosocial test
Bicycle	Weight-training	Sit		Psychosocial stress
Treadmill	Weight exercise	High intensity		Psychosocial task
Cycle ergometer	Weight-exercise	Moderate intensity		Stress task
Cyclergometer	Resistance exercise	Low intensity		Math task
Cycle-ergometer	Resistance training	Combined training		Speech task
Swimming	Strength	Combined exercise		Speech
Swim	Pilates	Concurrent training		Math
Running	Yoga	Concurrent exercise		Arithmetic
Run	Ioga			Arithmetic test
				Arithmetic task

Within each category, the terms were separated by union operators (i.e. "OR") and the categories were separated by parentheses and intersection operators (i.e. "AND").

Supplement table 2 – *Summary of sensibility analysis for blood pressure reactivity.*

Subgroup variables	Effect size					Subgroup differences p	Heterogeneity		
	SMD	95% CI	Weight (%)	k	m		i² (%)	τ²	Q
SBP stressor type									
Include physical stressor	-0.60	[-1.15; -0.04]	27.7	3	3		69	0.125	6.46*
Only mental stressor	-0.33	[-0.56; -0.10]	72.3	7	9	0.39	2	0.000	8.14
Overall effect	-0.42	[-0.65; -0.18]	100	10	12		35	0.048	16.85
DBP stressor type									
Include physical stressor	-0.24	[-0.71; 0.23]	19.8	2	2		19	0.000	1.23
Only mental stressor	-0.51	[-0.80; -0.22]	80.2	7	9	0.34	39	0.056	13.04
Overall effect	-0.45	[-0.70; -0.20]	100	9	11		33	0.045	14.99
SBP number of stressors									
Unique stressor	-0.32	[-0.56; -0.09]	66.6	6	8		13	0.001	8.05
Multiple stressors	-0.59	[-1.04; -0.14]	33.4	4	4	0.31	56	0.081	6.61
Overall effect	-0.42	[-0.65; -0.18]	100	10	12		35	0.048	16.85
DBP number of stressors									
Unique stressor	-0.48	[-0.79; -0.17]	74.2	6	8		42	0.061	12.07
Multiple stressors	-0.38	[-0.80; 0.04]	25.8	3	3	0.70	30	0.000	2.87
Overall effect	-0.45	[-0.70; -0.20]	100	9	11		33	0.045	14.99
SBP population									
Hypertensive only	-0.54	[-0.94; -0.13]	25.7	3	4		0	0.000	1.30
Normotensive only	-0.16	[-0.53; 0.21]	42.8	4	5	0.14	44	0.053	7.16
Both	-0.66	[-1.00; -0.32]	31.5	3	3		38	0.005	3.20
Overall effect	-0.42	[-0.65; -0.18]	100	10	12		35	0.048	16.85
DBP population									
Hypertensive only	-0.83	[-1.40; -0.26]	27.4	3	4		56	0.127	6.84
Normotensive only	-0.23	[-0.53; 0.08]	48.9	4	5	0.17	0	0.000	2.84
Both	-0.45	[-0.84; -0.06]	23.7	2	2		16	0.000	1.19
Overall effect	-0.45	[-0.70; -0.20]	100	9	11		33	0.045	14.99

*Include physical stressor: studies that used only physical stressors or in conjunction with mental stressors; SBP: systolic blood pressure; DBP: diastolic blood pressure; SMD: effect size by standardized mean differences; CI: credible interval; k: number of studies; m: number of comparisons; *: p<0.05.*

PRISMA 2020 checklist

Section and Topic	Item #	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	112
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	113
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	114
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	114
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	114-115
Information sources	6	Specify all databases, registers, websites, organizations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	115
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	115, 133
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	115-116
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	115-116
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	116
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	116
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	116-117
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	116-117
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis.	116-117
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	116-117
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	116-117
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	116-117
	13e	Describe any methods used to explore possible causes of heterogeneity among study results.	116-117
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	116-117

Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	116-117
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	-
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	115
	16b	Cite studies that met many but not all inclusion criteria ('near-misses') and explain why they were excluded.	119
Study characteristics	17	Cite each included study and present its characteristics.	118-119
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	124
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	121-122
Results of syntheses	20a	For each synthesis, briefly summarize the characteristics and risk of bias among contributing studies.	120, 123
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	121-122
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	123, 134
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	123, 87
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	124
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	-
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	124
	23b	Discuss any limitations of the evidence included in the review.	127
	23c	Discuss any limitations of the review processes used.	127
	23d	Discuss implications of the results for practice, policy, and future research.	127
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	114
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	114
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	116
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	128
Competing interests	26	Declare any competing interests of review authors.	128
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	128

CONCLUSÕES

A partir dos estudos expostos, chegamos as seguintes conclusões: **1)** o treinamento físico combinado pode ser usado para melhorar a pressão arterial e a modulação da frequência cardíaca de mulheres na pós-menopausa, independentemente da presença de hipertensão; **2)** a suplementação com isoflavonas não promove efeitos adicionais ao exercício físico na variabilidade de frequência cardíaca de mulheres após a menopausa; **3)** usuários de bloqueadores do receptor de angiotensina tem respostas mais pronunciadas ao treinamento físico combinado na PA sistólica de vigília, enquanto os usuários de β-bloqueadores apresentam respostas mais evidentes na variabilidade da pressão arterial; **4)** a reatividade da pressão arterial não difere entre usuários de bloqueadores do receptor de angiotensina e β-bloqueadores após exercício crônico; e **5)** tanto uma única sessão, quanto uma fase de treinamento com exercícios físicos, reduzem a reatividade da PA em testes de estresse.

Em suma, o exercício físico é uma estratégia eficaz para promover a saúde cardiovascular, tanto em repouso quanto sob situações de estresse, independente da presença de hipertensão ou do uso de isoflavonas, β-bloqueadores ou bloqueadores do receptor de angiotensina.

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ANEXO 1

Ambulatory blood pressure variability and combined exercise training: comparison between hypertensive and normotensive postmenopausal women

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Aim **The aim of the study was to verify the effects of moderate combined aerobic and resistance exercises training in ambulatory blood pressure (ABPM) and its variability in hypertensive and normotensive postmenopausal women.**

Methods **Twenty-six participants were divided into two groups: hypertensive (HT=13) and normotensive (NT=13). They performed 30 sessions of combined exercises (aerobic and resistance exercises at same session) over 10 weeks. We evaluated: resting BP and 24-h ABPM with systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), and heart rate (HR). To evaluate blood pressure variability (BPV), the following were considered: 24-h SD (SD_{24}), the mean diurnal and nocturnal deviations (SD_{dn}), average real variability (ARV_{24}).**

Results **The two-way analysis of variance showed no difference in ABPM nor BPV responses after training between groups. Both HT and NT groups had similar BP reductions in 24-h DBP ($P<0.01$; $\Delta NT=-3.1\pm1.1$, $\Delta HT=-1.8\pm1.2$ mmHg), 24-h area under the curve of DBP ($P=0.01$; $\Delta NT=-73\pm105$, $\Delta HT=-44\pm115$ mmHg), and wake DBP ($P<0.01$; $\Delta NT=-3.4\pm1.2$, $\Delta HT=-1.8\pm1.3$ mmHg), without differences in BPV responses. Moreover, HT women had higher overall SBP SD_{dn} ($P=0.01$), SBP ARV ($P=0.02$), and MBP ARV ($P<0.01$) than NT women.**

Conclusion **Ten-week combined exercise training resulted in similar BP reductions in hypertensive and normotensive postmenopausal women, but not in BPV responses.** *Blood Press Monit* **25: 338–345**

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Keywords: ambulatory blood pressure, blood pressure variability, combined exercise, menopause

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Introduction

Aging affects blood pressure (BP) in different ways in men and women. Premenopausal women have lower BP values than men, and after menopause, this situation reverses, with 41% of women becoming hypertensive [1–3]. The incidence increase of hypertension may be related to the nonproduction of estrogen by the ovaries, which causes an increase in sympathetic activity and vasoconstrictive adrenergic responsiveness [4,5].

In addition to its raw values, BP has short-term and long-term fluctuations. These variations can be understood as adaptations of humoral and neural systems to the environment and emotional stimuli, besides helping to diagnose changes in the mechanisms of BP regulation [6]. Thus, through ambulatory blood pressure monitoring (ABPM) it is also possible to evaluate the functioning of the autonomic nervous system by the analysis of blood pressure variability (BPV). High BPV values are related to an increased risk of cardiovascular events and a greater number of target organs lesions [7].

One of the best alternatives for treatment and prevention of hypertension is physical training, because it improves several cardiovascular parameters, such as reductions in SBP and diastolic blood pressure (DBP) values in hypertensive [8] and normotensive individuals [9], after short-term or long-term interventions [10], in addition, to reduce BPV especially in populations with cardiovascular dysfunction [11,12]. However, few studies have compared the BP responses to exercise on ambulatory and BPV measures after combined training (aerobic and resistance exercises at the same session).

Because combined training shows beneficial effects on several health parameters, it is recommended in the guidelines for prevention and treatment of hypertension [13,14]. However, it is worth noting that the magnitude

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and mechanisms of the exercise hypotensive responses may be different among normotensive and hypertensive individuals [15]. In addition, the effects of physical training on well-controlled hypertensives are still poorly understood, and antihypertensive drugs may influence the ability of the exercise to reduce BP [16]. Thus, the initial hypothesis was that BP reductions after moderate combined exercise training would be more pronounced in hypertensive women. Therefore, the aim of the study is to verify the effects of moderate combined aerobic and resistance exercises training in ambulatory BP and its variability in hypertensive and normotensive postmenopausal women.

Material and methods

Participants

This is a controlled clinical trial study, with BP assessments before and after 10 weeks of combined aerobic and resistance exercises training. Participants were divided into two groups: hypertensive (HT) ($n = 13$) and normotensive (NT) ($n = 13$). A total of 260 women, aged 50–70 years, postmenopausal (amenorrhea for at least 12 months) were recruited from traditional media, and 36 nonobese volunteers, who fulfilled the inclusion criteria and agreed to participate in the study. From the initial number of 36 women, 10 women did not complete the entire intervention, so 26 completed 10 weeks of training and perform posttests.

The inclusion criteria for the study were as follows: amenorrhea for at least 12 months; BMI ≤30 kg/m^2; ability to engage in treadmill and resistance exercises; no history of diabetes, cancer or cardiovascular disease (except for hypertension in HT); hypertension nonmedicated with beta-blockers; no hormone therapy or soy-derived supplementation; and nonsmokers. The Human Research Ethics Committee of the Federal University of Uberlândia approved this study (CAAE: 40622414.9.0000.5152). All volunteers signed a Consent Term. The experiments conformed to the principles set out in the World Medical Association Declaration of Helsinki and this research was registered at Clinicaltrials.gov (number: NCT03531034).

Evaluation of anthropometry

In the beginning, we indicated that the volunteers continued their eating habits until the end of the collections, so we performed a food intake analysis through dietary reminders of 24 h, applied by nutritionists on 3 nonconsecutive days. The dietary data analyses were performed using Dietpro (Minas Gerais, MG, Brazil) software (version 5.7i) and the United States Department of Agriculture (USDA) food composition table. This analysis demonstrated that there were no significant changes in macronutrient dietary patterns during 10 weeks of training (data not shown).

The body mass was measured using a Micheletti electronic scale (São Paulo, SP, Brazil), the stature was measured in a Sanny stadiometer (São Paulo, SP, Brazil) and an inelastic tape measuring 0.5 cm wide was used for abdominal circumference measurements. The bioelectrical impedance apparatus of Biodynamics model 450c (Biodynamics, Shoreline, Washington, USA) was used to estimate the total lean body mass, fat mass, and percentage of total body fat mass.

Resting and ambulatory blood pressures

Resting BP and heart rate (HR) was monitored through calibrated and validated automatic oscillometric monitors [17] (Omron HEM-7113, Shimogyo-Ku, Kyoto, Japan) in 3 nonconsecutive days. At pre and post moments, three measurements of systolic BP (SBP), diastolic BP (DBP), and HR were performed and considered as the mean for analysis. Values outside of two standard deviations from individual mean were discarded, being considered the average of the others.

All volunteers were submitted two times to a 24-h BP assessment by ABPM: before and after 10 weeks of combined exercise training, with a minimum of 48 h after the last training session. An ABPM Cardios Dyna-MAPA + device (São Paulo, SP, Brazil) was used associated with a self-report diary of activities of daily living (sleep, work, food, etc.) or any event that could interfere abnormally with BP or device measurements. The device was always placed in the morning (7:00 a.m.) and the measurements were made every 15 min from 7:00 to 23:00 and every 30 min from 23:00 to 7:00. Before use ABPM during daily activities, resting BP was measured using the same equipment after 15 min of rest in sitting position. The monitoring was considered effective when at least 80% of the measures were valid. To analyze the BP curve from 0 to 24 h, it was adopted as time 0 the moment in which the monitor was placed. The following results were evaluated: SBP, DBP, mean blood pressure (MBP) and HR divided into awake, sleep, and 24-h phases.

Blood pressure variability

Based on ABPM data, BPV was calculated using three different parameters[18]: 24-h SD weighted by the time interval between consecutive readings (SD_{24}); the mean diurnal and nocturnal deviations weighted for the duration of the daytime and nighttime interval (SD_{dn}); the average real variability (ARV) weighted for the time interval between consecutive readings.

Exercise program

The exercise program consisted of 30 sessions of combined aerobic and resistance exercises training distributed over 10 consecutive weeks. Each session lasted 45 min and consisted of 5 min warm-up on a treadmill, 20 min of resistance exercise, and 20 min of aerobic

exercise. The resistance training was performed using 60% of one maximal repetition test (1RM), that was previously evaluated according to with Kraemer and Fry [19] protocol, in two sets of 15 repetitions in seven exercises of weight training for large muscle groups: Leg press 45°, seated cable row, vertical chest press machine, seated fly machine, wide grip lat pull-down, squat (with lumbar swiss ball support), and abdominal crunch. The aerobic exercise was performed on treadmill, at a speed of 5.5 km/h and intensity (imposed by treadmill inclination and HR) between ventilatory thresholds 1 and 2 intensities, determined through a test protocol adapted from Puga *et al.* [20]. After 5 weeks of training, 1RM test was performed again to readjust the resistance training load and aerobic intensity was readjusted by HR predicted in the incremental test.

Statistical analysis

Sample calculation ($n = 24$) was performed in G-Power 3.1 software (Effect size f: 0.3; α err: 0.05; power: 0.80). The results are presented as means ± SD. The data distribution was analyzed using the Shapiro–Wilk test and the variances homogeneity was assessed by the Levene test. Variables without normality or homogeneity were transformed into Log and later in *Z*-score until assuming these assumptions. The two-way analysis of variance for repeated measures was used to analyze the time (pre and post) and group (HT and NT) interactions with a Bonferroni post hoc test, when appropriate. Unpaired Student's *t*-tests were used to compare variables with only one measurement over time (age, height, and time after menopause) between groups. BP variation over time was analyzed by the area under the curve (AUC) calculated by the trapezoidal method in GraphPad Prism Software version 6. Statistical significance was set as $P < 0.05$. Statistical Package for the Social Sciences version 20.0 (SPSS Inc., Chicago, Illinois, USA) was used for all analyses.

Results

Most hypertensive volunteers used angiotensin-2 AT-1 receptor blocker, associated (30.8%) or not (30.8%) with thiazide diuretics, then we have users of angiotensin-converting enzyme inhibitors, associated (7.7%) or not (15.4%) with thiazide diuretics, and finally, we have users of thiazide diuretics as monotherapy (15.4%).

Among general characteristics, only age presented a statistical difference between groups ($P = 0.003$; HT – 52.7 ± 5.3; NT – 58.9 ± 3.9 years). Other basal characteristics such as time post-menopause ($P = 0.457$; HT – 4.7 ± 3.9; NT – 5.9 ± 3.9 years) and height ($P = 0.622$; HT – 1.57 ± 0.05; NT – 1.58 ± 0.08 m) did not show differences by *t*-test. The maximum strength evaluation by 1-RM test demonstrated time effects ($P < 0.01$) with no interaction or group effects in the upper (i.e. bench press; ΔHT – 10.00 ± 7.36; ΔNT – 9.69 ± 3.92 kg) and lower limbs (i.e. leg press; ΔHT – 58.08 ± 68.57; ΔNT – 82.85 ± 32.59 kg).

Table 1 shows general characteristic differences between groups and times. These analyses showed interaction effect in body mass ($P = 0.04$). However, body composition analysis did not show interaction or group effects, but rather effects of time, with reductions of fat mass ($P = 0.01$) and percentage of fat ($P = 0.01$), as well as increases in lean mass ($P = 0.01$) in both groups. Similarly, resting BP and HR analyzes did not show interaction or group effects, but rather effects of time, with reductions of SBP ($P = 0.03$) and DBP ($P = 0.02$), without statistical effects in HR.

Table 2 shows comparisons of ambulatory BP. There are no interaction effects at any analyzed variable. In 24-h parameters, it was possible to observe time effects on DBP ($P < 0.01$) with lower values at post-training in both groups. On sleep parameters, there were group effects on DBP ($P = 0.04$) and MBP ($P = 0.01$), with higher values on HT. Additionally, on wake DBP it was possible to observe time effects ($P < 0.01$) with lower values at post-training in both groups. There was no significant difference among time variations (Δ) in all parameters evaluated.
Table 3 shows BPV data. There are no interactions or time effects at any variable. It was possible to observe group effects on SBP SD_{dn} ($P = 0.01$), ARV SBP ($P = 0.02$), and ARV MBP ($P < 0.01$) with higher values on HT.
In Fig. 1, panels A and B present 24-h values used to AUC calculation of SBP and DBP, respectively; panels C and D present the values of AUC of SBP and DBP, respectively. No significant Interaction or group effects were found in any of the investigated parameters. On the other hand, it was possible to observe time effects on DBP ($P = 0.012$) with lower values at post-training in both groups.

Discussion

The present study demonstrates that 10 weeks of combined moderate-intensity exercise were able to improve BP in both groups, without a significant difference between them. After 10 weeks, there was a reduction (time effects) in 24-h DBP, Wake DBP, AUC SBP, and AUC DBP, but there was no change in BPV parameters in both groups. In addition, there were group effects, with higher HT values in ABPM (sleep SBP, DBP, and MBP) and its variability (24-h MBP, SD_{dn} SBP, ARV SBP, ARV DBP, and ARV MBP).

Another important result of the present study was that the effects of the training were better evidenced in awake compared to sleep phase. Similar result was found in the short-term [21], in which on the day of the exercise there was no reduction during night. According to a meta-analysis, this kind of response was verified in normotensive and hypertensive adults [8]. Possibly, these response pattern is related to reduction of sympathetic activity [22], which during the sleep period is naturally reduced.

Table 1 General characteristics

	Pre-mean±SD	Post-mean±SD	Δ Mean±SD	*P* groups	*P* time	*P* inter.
Body mass (kg)						
HT	68.51±8.30	67.70±8.14	−0.81±0.68	0.43	0.66	0.04
NT	64.82±8.99	66.06±9.08	1.24±3.43			
BMI (kg/m^2)						
HT	27.68±4.57	27.36±4.56	−0.32±0.28	0.72	0.56	0.12
NT	26.89±2.91	27.03±3.40	0.15±1.02			
Abdominal circumference (cm)						
HT	93.61±9.21	93.44±8.62	−0.17±2.61	0.64	0.08	0.14
NT	92.92±7.91	91.00±8.06	−1.92±3.17			
Body fat (%)						
HT	38.42±6.98	37.32±7.34	−1.10±1.61	0.20	0.01	0.71
NT	35.38±3.74	34.52±4.08	−0.86±1.66			
Fat mass (kg)						
HT	26.50±6.91	25.69±6.95	−0.81±1.17	0.16	0.01	0.51
NT	23.03±4.60	22.53±4.75	−0.51±1.14			
Lean mass (kg)						
HT	39.20±4.00	39.88±4.22	0.68±1.00	0.15	0.01	0.83
NT	41.60±4.01	42.19±3.90	0.59±1.05			
Systolic blood pressure at rest (mmHg)						
HT	121.84±13.68	120.38±6.56	−1.5±12.9	0.52	0.03	0.09
NT	129.08±17.39	119.23±13.13	−9.8±11.3			
Diastolic blood pressure at rest (mmHg)						
HT	76.31±8.09	75.38±7.71	−0.8±7.1	0.14	0.02	0.07
NT	84.31±12.17	77.77±9.29	−6.5±8.1			
Heart rate at rest (mmHg)						
HT	71.46±9.77	67.61±7.00	−3.9±8.5	0.22	0.51	0.13
NT	73.08±10.94	74.61±11.15	1.5±9.1			

BMI, body mass index; HT, hypertensive group; inter., interaction effect; NT, normotensive group.

Table 2 Ambulatory blood pressure monitoring

	Pre-mean±SD	Post-mean±SD	Δ Mean±SD	*P* groups	*P* time	*P* inter.
24-h SBP (mmHg)						
HT	122.4±9.8	119.5±7.7	−2.9±2.2	0.18	0.06	0.98
NT	117.7±10.8	114.9±9.6	−2.7±1.9			
24-h DBP (mmHg)						
HT	75.7±6.2	73.8±6.3	−1.8±1.3	0.25	<0.01	0.42
NT	73.5±7.5	70.1±7.1	−3.4±1.2			
24-h MBP (mmHg)						
HT	93.5±5.0	92.7±6.2	−0.7±1.8	0.05	0.13	0.36
NT	89.8±8.6	86.6±7.3	−3.2±1.7			
Sleep SBP (mmHg)						
HT	115.8±10.9	112.6±11.5	−3.5±3.2	0.05	0.41	0.51
NT	106.8±10.7	106.4±11.2	−0.5±2.8			
Sleep DBP (mmHg)						
HT	69.7±7.4	67.1±7.5	−2.6±2.3	0.04	0.24	0.56
NT	63.5±7.7	62.6±7.9	−0.9±1.8			
Sleep MBP (mmHg)						
HT	87.4±6.3	85.9±9.4	−1.5±2.8	0.01	0.51	0.90
NT	79.8±8.2	78.8±8.3	−0.9±2.4			
Wake SBP (mmHg)						
HT	124.5±10.0	121.6±7.1	−2.9±2.2	0.40	0.07	0.84
NT	121.2±11.6	118.9±9.0	−2.2±1.7			
Wake DBP (mmHg)						
HT	77.6±6.2	75.8±6.7	−1.8±1.2	0.46	<0.01	0.44
NT	76.3±8.1	73.1±7.0	−3.1±1.1			
Wake MBP (mmHg)						
HT	95.5±5.0	94.8±5.7	−0.7±1.7	0.18	0.13	0.35
NT	93.1±9.3	90.2±7.2	−2.8±1.5			

DBP, diastolic blood pressure; HT, hypertensive group; inter., interaction effect; MBP, mean blood pressure; NT, normotensive group; SBP, systolic blood pressure.

Behavioral changes are recommended for control and prevention of arterial hypertension, among them: weight reduction, control of sodium and alcohol consumption, and regular physical exercise. These changes appear to have distinct quantitative and qualitative effects on BP but potentialized when performed together [23]. Among these strategies, we highlight moderate combined training, that is recommended as a nonpharmacological strategy in various guidelines [13,14,24], that show hypotensive responses mainly in DBP [8], but promising results also in SBP [16]. On the other hand, it is important to highlight that are recommendations for exercise doses, because the hypotensive responses are dependents of the intensity, volume, and duration of the exercise, in addition to baseline BP values [8]. In this sense, exercise with moderate intensity for hypertensive patients after

Table 3 Blood pressure variability

	Pre-mean±SD	Post-mean±SD	Δ Mean±SD	*P* groups	*P* time	*P* inter.
SD_{24} SBP (mmHg)						
HT	12.7±2.1	13.0±2.0	0.3±0.5	0.35	0.78	0.48
NT	12.3±4.3	11.7±2.7	−0.7±1.2			
SD_{24} DBP (mmHg)						
HT	9.4±1.5	10.1±1.3	0.6±0.5	0.30	0.27	0.37
NT	9.7±2.1	9.9±2.2	0.2±0.8			
SD_{24} MBP (mmHg)						
HT	9.8±2.0	10.0±1.6	0.2±0.6	0.75	0.99	0.77
NT	9.8±2.9	9.6±2.3	−0.2±1.0			
SD_{dn} SBP (mmHg)						
HT	11.6±1.0	12.2±2.1	0.5±0.4	0.01	0.78	0.37
NT	10.3±2.6	10.0±2.0	−0.3±0.8			
SD_{dn} DBP (mmHg)						
HT	8.5±1.4	9.0±1.3	0.4±0.4	0.17	0.10	0.59
NT	7.7±1.3	8.6±2.0	0.9±0.7			
SD_{dn} MBP (mmHg)						
HT	8.8±1.6	9.0±1.3	0.1±0.4	0.07	0.56	0.73
NT	7.7±1.6	8.1±1.9	0.4±0.7			
ARV SBP (mmHg)						
HT	10.7±1.2	10.2±1.9	−0.5±0.3	0.02	0.52	0.46
NT	9.1±1.2	9.1±2.3	0.03±0.7			
ARV DBP (mmHg)						
HT	7.7±1.3	8.0±1.5	0.3±0.4	0.05	0.28	0.98
NT	6.6±1.3	7.0±1.2	0.3±0.4			
ARV MBP (mmHg)						
HT	7.7±1.2	7.5±1.3	−0.2±0.4	<0.01	0.91	0.45
NT	6.4±1.0	6.6±1.1	0.2±0.4			

ARV, the average real variability weighted for the time interval between consecutive readings; DBP, diastolic blood pressure; HT, hypertensive group; inter., interaction effect; MBP, mean blood pressure; NT, normotensive group; SBP, systolic blood pressure. SD_{24}, 24-h SD weighted by the time interval between consecutive readings; SD_{dn}, the mean diurnal and nocturnal deviations weighted for the duration of the daytime and nighttime interval.

menopause has positive aspects related to exercise tolerance and adherence to training [22], also being sufficient to provide significant changes in BP [25,26] and BPV [27] after its performance.

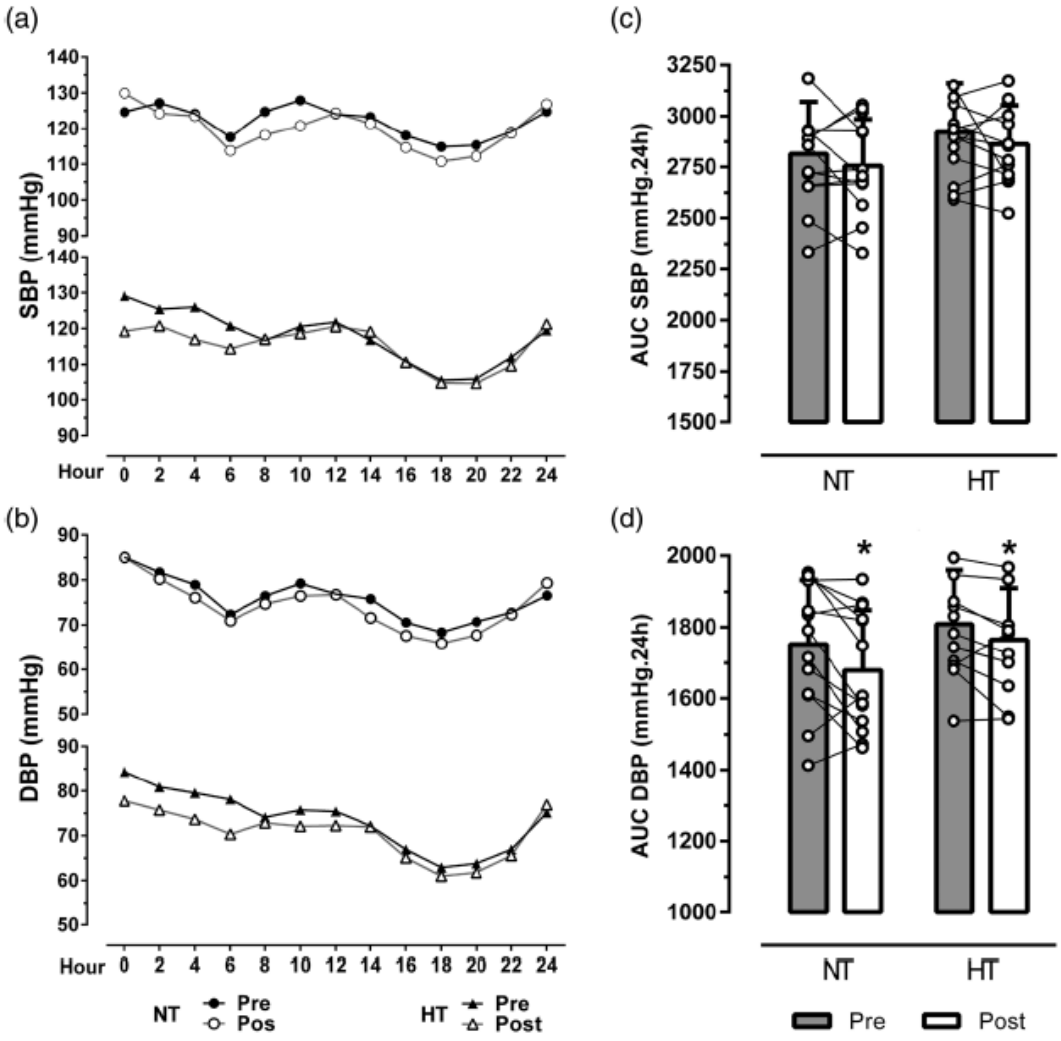
It is known that physical training improves aerobic fitness and physiological adaptations to cardiovascular health in hypertensive and normotensive patients, including postmenopausal women [9], and is able to reduce the risk of cardiovascular diseases from 30 to 40% in all populations [22]. Although no significant difference between groups was demonstrated, the effect of combined training was beneficial for both, since reductions around 5 mmHg of SBP and 2 mmHg of DBP are sufficient to reduce the risk of stroke in 13 and 11.5%, respectively [28], similar values to those found in the present study especially in ambulatorial DBP. Comparable results with normotensive women were found in other studies, such as those performed by Mandrup *et al.* [29], in which 3 months of training demonstrated DBP reduction and other health parameters improvements in postmenopausal women, being a group predisposed to develop cardiovascular diseases, the exercise acts as a prevention of hypertension and other health risk factors [22].

Previous studies [30] have also found significant hypotensive responses after conducting combined training in hypertensive postmenopausal women, but with greater magnitude, which may be related to the higher baseline values (SBP – 152 mmHg, DBP – 95 mmHg) in comparison with those of the present study (SBP – 122 mmHg, DBP – 76 mmHg). Although hypertensive, and with values significantly higher than the NT group, baseline 24-h BP values were still close to the recommended values, which may influence the magnitude of the hypotensive response after training in the present study.

Concerning the possible physiological mechanisms responsible for these BP falls, a recent review [22] describe various of these mechanisms, which can have central action as increased baroreflex sensitivity and reduction of autonomic dysfunction, with increase vagal tonus and reduction of sympathetic tone; or peripherical action as improvements of endothelial function induced by serum increase of vasodilators such as acetylcholine and bradykinin, improvements in nitric oxide metabolism due to increased enzymatic activity and phosphorylation of nitric oxide synthase enzyme, as well as increases in nitrite/nitrate and nitrogen oxide serum concentrations that cause endothelium-dependent vasodilation, reduced vascular resistance and improved arterial stiffness in peripheral arteries.

In addition to reduce BP, these variations in vascular activity are closely related to improvements in BPV caused by exercise [27] and antihypertensive drugs [31]. It is worth noting that there are pieces of evidence that the magnitude of BPV is independent of BP absolute levels and correlates closely with target organ damage and with the incidence of cardiovascular events [11]. Therefore, physical exercise in postmenopausal women attenuates arterial aging, promoting important functional vascular

Fig. 1



Twenty-four-hour blood pressure (BP) and the correspondent area under the curve. (panels a and b) Mean values of systolic and diastolic BP, respectively. (panels c and d) Values of 24-h area under the curve of systolic and diastolic BP, respectively, in these panels the circles connected by lines represent individual values. AUC, area under the curve; DBP, diastolic blood pressure; HT, hypertensive group; NT, normotensive group; SBP, systolic blood pressure; *: time effect ($P<0.05$).

adaptations, such as reduction of arterial stiffness [22] in this population. In addition, the structural adaptations that allow distension of the arterial wall obtained with physical exercise are fairly stable, which makes it possible to maintain BP values close to the recommended [3,32].

A possible mechanism that may explain the absence of improvement after training is the loss of estrogen after menopause, which appears to be linked to a decrease in β-adrenergic vasodilation and an increased risk of hypertension in older women [4], attenuating responses in both groups. Other important factors that contribute to mitigating BPV differences between groups are obesity and arterial stiffening associated with aging [33]. Specifically for HT, the use of antihypertensive drugs capable to improve BPV, like angiotensin receptor blockers [34] (those predominant in the present study), may have saturated the mechanism of action of exercise training given the endothelium-dependent mechanism of both [27,31], preventing more pronounced responses in this group. On the other hand,

the group effects found on ambulatory BP and BPV corroborate with that found in the literature [35], in which hypertensive women, have higher baseline BP and BPV than normotensive women. So, these differences can be explained by the worse vascular and autonomic health associated with hypertension [22].

In view of what has been shown, we note that this study has limitations that should be highlighted. First, it is a small sample ($n = 26$), which in view of the high prevalence of hypertension worldwide may have difficulties in generalizing under different circumstances. However, it is worth note that the final sample is in accordance with the initial sample calculation. Furthermore, we did not standardize antihypertensive drugs and their doses, but the volunteers had to stay with the same drug and dose throughout the study. Although there was a significant difference in age between HT and NT groups, and this difference could influence BP responses due to vascular aging, we highlight that women in both groups were middle-aged (age between 50 and 60 years), and they were with similar time after menopause, probably in the same climacteric phase. Finally, the lack of groups without physical training can limit the comprehension of the effects of exercise. However, BP reductions after physical exercise training have already been demonstrated in the literature extensively [15,16,26,36] with different populations (men, women, youth, elderly, healthy, or sick) and exercise characteristics (aerobic, resistance, isometric, combined, etc.) which we believe that minimizes the idiosyncratic problems of our experimental design. Thus, these results cannot be generalized to men, women in different stages of life and climacteric, users of antihypertensive drugs different from those presented or with different characteristics of physical training.

Conclusion

Ten weeks of moderate combined aerobic and resistance exercise training resulted in similar reductions in ambulatory BP in both hypertensive and normotensive postmenopausal women, although it results in no effect on BP variability.

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Registration number on clinical trials: NCT03531034.

Conflicts of interest

There are no conflicts of interest.

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ANEXO 2

Acute and Chronic Effects of Exercise in Health

Effect of combined exercise training on heart rate variability in normotensive and hypertensive postmenopausal women

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Abstract - Aim: This study aimed to verify and compare the effects of 10 weeks of combined exercise training on the heart rate variability of normotensive (NT) and hypertensive (HT) postmenopausal women. **Methods:** This is a quasi-experimental controlled clinical trial. Therefore, 14 HT and 12 NT postmenopausal women completed 10 weeks of combined exercise training. The exercise protocol consisted of 45 min of exercise, performed 3 times a week, consisting of 5 min of warm-up, 20 min of resistance exercise, and 20 min of aerobic exercise. Heart rate variability assessments were performed before and after the end of physical training. **Results:** Heart rate variability was assessed pre- and post-training periods. Mean RR ($\Delta NT = 95 \pm 88$; $\Delta HT = 38 \pm 127$), SDNN ($\Delta NT = 9 \pm 13$; $\Delta HT = 3 \pm 14$), RMSSD ($\Delta NT = 10 \pm 12$; $\Delta HT = 2 \pm 18$), SD1 ($\Delta NT = 7 \pm 8$; $\Delta HT = 1 \pm 13$), and SD2 ($\Delta NT = 10 \pm 18$; $\Delta HT = 4 \pm 17$) showed improvements after the intervention (time effects $p < 0.05$). No parameters presented group or interaction effects ($p \geq 0.05$). **Conclusion:** In summary, 10 weeks of combined exercise training improved heart rate variability parameters similarly in both NT and HT postmenopausal women. Therefore, combined exercise training may be used to improve autonomic modulation of the heart rate of postmenopausal women, regardless of the presence of hypertension.

Keywords autonomic nervous system, aerobic exercise, resistance exercise, blood pressure.

Introduction

Heart rate variability (HRV) is a non-invasive measurement to evaluate the autonomic modulation of heart rate (HR)[1,2]. Decreased HRV is related to an increased risk of arrhythmia and sudden cardiac death[1]. Although HRV decreases with aging[3], this effect is pronounced after menopause[4,5], when the decreased level of estrogen may interfere with the modulation of cardiovascular autonomic control[6]. Therefore, it is relevant to investigate strategies capable of improving HRV in these women.

The benefits of physical exercise training to improve HRV have been previously reported in meta-analyses[7-10]. In postmenopausal women, the positive effect of isolated aerobic exercises[11] and combined with resistance exercises training (i.e. combined exercise training; CET)[12] to improve HRV have already been reported. In addition to the benefits of CET with regard to cardiac autonomic control, this kind of exercise is recommended by the American College of Sports Medicine to maintain and improve cardiovascular and muscular health and functioning of healthy and old adults[13,14]. Furthermore, CET may positively influence systemic inflammation and oxidative stress, bone health, and climacteric symptoms related to being postmenopausal[15,16]. These factors encourage postmenopausal women to include CET as a training strategy in their lives.

In postmenopausal women, the incidence of hypertension is higher compared to men of a similar age and women before menopause[17]. It is part of the risk groups of cardiovascular diseases, which are the main causes of mortality in the world[18]. Previous studies have shown that hypertensive (HT) patients presented worse HRV indices compared to normotensive (NT) subjects, indicating poor cardiac autonomic control[12,19]. The CET, in turn, may improve HRV parameters in HT premenopausal women[20]. However, in HT postmenopausal women, the effect of CET on HRV has not yet been shown. Furthermore, although CET may have a positive effect on the HRV of NT postmenopausal women[12], studies are necessary to identify if similar benefits could be reported in HT postmenopausal women.

This study aimed to verify the effects of 10 weeks of combined exercise training on the HRV of normotensive and hypertensive postmenopausal women and compare

the responses between these groups. The hypothesis is that CET would improve HRV parameters in both HT and NT postmenopausal women, with higher improvements in HT subjects. This hypothesis was raised since HT subjects could have had a reduced HRV compared with NT subjects[21,22], presenting more sensibility to the training.

Methods

Experimental approach to the problem

This is a quasi-experimental controlled clinical trial study, in which HRV was monitored in the HT and NT groups before and after 10 weeks of CET. An incremental treadmill test was performed a minimum of 72 h before the first day of training to identify the intensity of aerobic training. Body mass, height, and body mass index were measured before treadmill testing. Pre-, post-5 weeks, and post-10 weeks of training, participants performed the one maximum repetition test (1RM) to identify the resistance training workload. All tests were performed respecting 48 h without exercise and a minimum of 48 h between tests. HRV recording was performed before and after 10 weeks of training, respecting 48 h without exercise. The study design is presented in Figure 1. The privation of caffeine and alcohol for 24 h was required for all tests.

Subjects

A total of 383 postmenopausal women, aged 50-70 years, recruited from traditional media (TV, radio, and posters) in 2015 and 2016 agreed to participate, of which 40 fulfilled the inclusion criteria. The entire study was carried out at the Federal University of Uberlândia. So, 26 subjects (14 hypertensive [HT] and 12 normotensives [NT]) completed the training (Figure 2). The inclusion criteria were amenorrhea for at least 12 months; body mass index $\leq$ 30 kg/m^2; ability to engage in treadmill and resistance exercises; no history of diabetes, cancer, or cardiovascular disease (except for hypertension); not using beta-blockers; no hormone therapy; and non-smokers. This study was approved by the local ethics committee (CAAE: 40622414.9.0000.5152), and all volunteers were informed of the benefits and risks of the investigation prior to signing informed consent agreeing to participate. This research has been conducted in accordance with the principles set forth in the Helsinki Declaration and was registered at Clinicaltrials.gov (number: NCT03531034). The present study presents secondary data from this registry of which the primary data have already been published[23].

The International Physical Activity Questionnaire short-form (IPAQ) was used to evaluate the initial level of physical activity of the volunteers. All participants were instructed to maintain their regular eating habits throughout the study. Furthermore, a food intake analysis through 24-h dietary records was applied by nutritionists on three non-consecutive days before and after training. The dietary data analyses were performed using a web-based program (DIETPRO® 5.7i; Minas Gerais, MG, Brazil) and the United States Department of Agriculture food composition table. This analysis demonstrated that there were no significant changes in dietary patterns during the training (data not shown).

Procedures

Resting blood pressure was monitored through calibrated and validated automatic monitors[24] (OMRON® HEM-7113, Shimogyo-Ku, Kyoto, Japan) on three non-consecutive days. At each moment, three measurements of systolic BP (SBP) and diastolic BP (DBP) were performed, and the mean was considered for analysis.

The incremental treadmill test was adapted from Puga et al.[25]. Briefly, all volunteers performed a submaximal incremental test on a treadmill at 5.5 km/h, and the intensity was increased using treadmill inclination (1% every 2 min) until volunteers reached 85% of their predicted maximum HR or 18 of perceived exertion using the Borg Scale. Oxygen uptake and carbon dioxide output were recorded during all tests using a gas analyzer (COSMED QUARK CPET gas analyzer, Rome, Italy). The goal of this test was to identify ventilatory thresholds based on ventilatory equivalents.

The intensity of resistance exercise was evaluated and prescribed based on the 1RM[26]. This test consisted of a warm-up of two sets of the exercise to be performed at intensities around 50% and 80% of the subjective estimate of 1RM, with eight and three repetitions, respectively. After this, a maximum of five attempts per exercise was allowed to find the highest workload at which the volunteer could only make one full movement with a 3-min rest between attempts[26].

Resting R-R intervals were recorded for 20 min in the seated position using an HR monitor (POLAR®

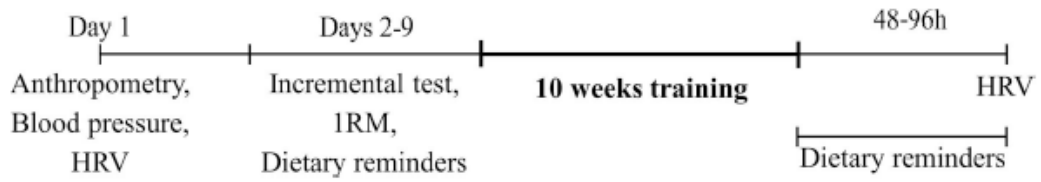

Figure 1 - Study design. HRV: heart rate variability; 1RM: one maximum repetition test.

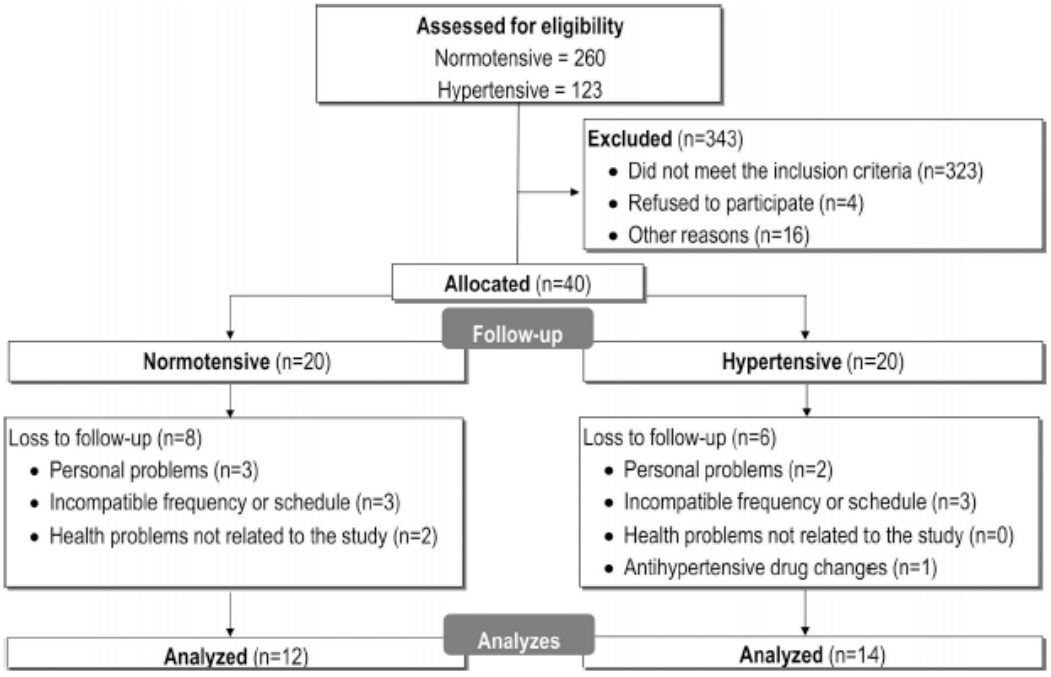

Figure 2 - Follow-up flowchart.

RS800cx; Polar Electro Oy, Finland; sampling frequency = 1000 Hz) with spontaneous breathing. Data were downloaded to a computer using an infrared interface with specific software (POLAR PRO TRAINER5®, Polar Electro, Kempele, Finland). HRV analysis was performed using KUBIOS HRV 3.0 (University of Kuopio, Kuopio, Finland)[27]. Prior to the analysis, the signal was visually inspected and filtered, and a range of 5 min with few artifacts was selected close to the end of the recording for analysis.

The resulting R-R intervals were analyzed in the time domain, in the frequency domain using spectral analysis (Fast Fourier Transform), and nonlinearly through the Poincaré plot[27]. The time-domain indices analyzed included the square root of the mean squared difference of successive R-R intervals (RMSSD), the standard deviation of all normal R-R intervals recorded at an interval of time (SDNN), and the percentage of pairs of adjacent RRi differing by more than 50 ms in the whole recording (pNN50). In the frequency domain, the data series were interpolated at 4 Hz, after which removal of the signal linear trend component was performed using the smooth prior approach.

In the frequency domain, oscillations of R-R intervals were examined within the low-frequency (LF: 0.04-0.15 Hz) and high-frequency bands (HF: 0.15-0.40 Hz). LF and HF were expressed in normalized units. The sympathovagal balance was obtained through the ratio of the LF to HF (LF/HF) bands[1]. For nonlinear indices, the Poincaré plot was examined, and the transversal (SD1) and longitudinal (SD2) axes of the ellipse-like dispersion were calculated.

The exercise program consisted of 30 sessions of combined exercise training performed over 10 consecutive weeks. Each session lasted 45 min and consisted of 5 min of warm-up on a treadmill (5.5 km/h and 0% inclination), 20 min of resistance exercise, and 20 min of aerobic exercise. The resistance training was performed in two sets of 15 repetitions at 40% of 1RM with 1 min intervals in seven exercises for large muscle groups: leg press 45°, seated low row, vertical chest press, pec deck, wide grip lat pull-down, Swiss ball squat, and abdominal crunch. The aerobic exercise was performed on a treadmill at a velocity of 5.5 km/h with an intensity (imposed by the treadmill inclination test reported above) between ventilatory thresholds 1 and 2. After 5 weeks of training, the intensity of the resistance training was adjusted based on a new 1RM, and the intensity of the aerobic exercise was readjusted through a 20% increase in treadmill inclination.

Statistical analysis

The sample calculation (mininum n = 24) was performed in G-Power 3.1 (Universität Düsseldorf, Germany) software (α error = 0.05 and power = 0.80), considering

RMSSD as the mean variable and 10.3 ± 17.0 ms as possible variations in this index after a medium intensity training phase in postmenopausal women[20]. A Cohen's d of 0.6058 was found, which was then transformed into effect size f for the sample calculation (0.3029). Characteristics and anthropometric values were compared by the t-test for independent samples. Frequencies of physical activity levels were compared using the Chi-square test with the exact Monte Carlo test when the expected count was less than 5. The normality of data was tested using the Shapiro-Wilk test. A two-factor (time and group) generalized estimating equation technique (GEE) was performed for between, within, and interaction comparisons. Mean RR, LF, HF, and SD2/SD1 presented normality and were analyzed using a linear model. Since some data of pNN50 presented values of 0, this variable was analyzed using a linear model. Other variables were analyzed using the gamma with log link model. All analyses were performed using IBM® SPSS® Statistics 20. The significance level adopted was $p < 0.05$.

Results

Table 1 shows the anthropometric, activity level, and drug characteristics of the volunteers. There was a difference only in age, which was higher in the HT group compared with the NT group. HRV parameters (mean and standard deviation) are described in Table 2. Mean RR ($p < 0.01$), SDNN ($p = 0.03$), RMSSD ($p = 0.03$), SD1 ($p = 0.03$), and SD2 ($p = 0.04$) showed time effects (Table 2). No parameters had group ($p > 0.05$) or interaction ($p > 0.05$) effects.

Discussion

The present study hypothesized that CET could promote greater improvement in HRV in HT postmenopausal women compared with NT postmenopausal women. Our results refute this hypothesis since we found no differences between NT and HT postmenopausal women in adaptations to CET in mean RR, SDNN, RMSSD, SD1, and SD2.

A greater effect of CET on the HRV of HT postmenopausal women was expected, because the cardiac autonomic modulation of HT subjects at rest was impaired, reflecting in lower general and vagal parameters of HRV[21,22]. For example, the overall variability measured by SDNN can be up to 15% lower in HT when compared to healthy ones[21]. Apparently, a trainability effect was expected on HRV, with subjects with lower HRV having a higher effect with training[28]. This improvement can reach up to 50% of the overall variability measured by SDNN after combined training in women[20]. However, participants of the present study presented well-controlled hypertension (SBP: 121.8 ± 13.1 mm Hg; DBP: 76.0 ± 7.8 mm Hg), which may have mitigated the autonomic differences between the HT and NT groups (Table 2). So, the use of antihypertensive drugs may explain why we did not find statistical differences between the groups. However, only the use of atenolol, with or without amlodipine, is related to modifications in HRV at rest in HT patients[29], which is a family of medicines not used by subjects in the present study. Therefore, additional studies are desired to investigate if antihypertensive drugs may affect rest HRV as well as the effect of exercise training on the HRV of HT postmenopausal women. Up to now, the results suggest no

Table 1 - Anthropometric, activity level, and medical characteristics of normotensive and hypertensive groups. Data are presented in Mean ± Standard Deviation or frequency (% within the group).

	NT (n=12)	HT (n=14)	p (t test)		NT (n=12)	HT (n=14)
Characteristics				Antihypertensives		
Age (years)	53.1 ± 5.3	58.7 ± 3.8	<0.01	ACEi (n)	–	1 (7.1)
Amenorrhea (years)	5.0 ± 3.9	7.2 ± 6.2	0.30	ACEi + Diuretic (n)	–	1 (7.1)
SBP (mmHg)	128 ± 18	122 ± 13	0.30	ARB (n)	–	4 (28.6)
DBP (mmHg)	84 ± 13	76 ± 8	0.06	ARB + Diuretic (n)	–	5 (35.7)
Anthropometrics				Thiazide Diuretic (n)	–	3 (21.4)
Height (m)	1.57 ± 0.06	1.58 ± 0.07	0.60			
Body Mass (kg)	64.9 ± 9.4	69.2 ± 8.4	0.22	Other medicines		
BMI (kg/m^2)	26.9 ± 3.0	27.9 ± 4.5	0.53	Calcium (n)	1 (8.3)	3 (21.4)
Physical Activity level			p (X^2)	Statin (n)	2 (16.6)	3 (21.4)
Sedentary (n)	–	–	0.33	Anti-depressant (n)	–	2 (14.3)
Irregularly active (n)	7 (58.3)	6 (42.9)		PPI (n)	–	1 (7.1)
Active (n)	4 (33.3)	8 (57.1)		Beclomethasone (n)	–	1 (7.1)
Very active (n)	1 (8.3)	–		Levothyroxine (n)	1 (8.3)	–

NT: Normotensive group; HT: Hypertensive group; SD: Standard deviation; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; ACEi: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin 1 receiver blockers; PPI: Proton pump inhibitor.

Table 2 - Heart rate variability parameters on normotensive and hypertensive postmenopausal women.

	Groups	Pre (mean ± SD)	Post (mean ± SD)	p Group	p Time	p Interaction
Mean RR	NT	760.12±104.59	855.31±114.19	0.50	<0.01	0.16
	HT	813.44±132.19	851.33±87.06			
SDNN	NT	20.95±14.35	29.68±17.25	0.69	0.03	0.31
	HT	21.77±12.19	24.73±8.99			
RMSSD	NT	15.64±11.40	25.88±14.87	0.60	0.03	0.12
	HT	21.39±15.98	23.36±9.64			
pNN50	NT	2.43±6.71	8.05±10.51	0.64	0.48	0.05
	HT	7.95±13.17	5.34±6.80			
LF	NT	73.66±9.48	67.62±18.19	0.29	0.66	0.36
	HT	65.02±21.82	67.14±13.78			
HF	NT	26.27±9.47	32.28±18.12	0.29	0.66	0.36
	HT	34.86±21.78	32.80±13.78			
SD1	NT	11.09±8.08	18.35±10.54	0.60	0.03	0.12
	HT	15.15±11.32	16.55±6.83			
SD2	NT	27.43±18.75	37.31±22.74	0.52	0.04	0.46
	HT	26.38±13.75	30.54±11.31			
SD2/SD1	NT	2.63±0.63	2.22±0.78	0.07	0.11	0.59
	HT	2.18±0.85	1.98±0.56			

NT: Normotensive group; HT: Hypertensive group; SDNN: Standard deviation of normal RR intervals; RMSSD: Root Mean Square of the Successive Differences of RR intervals; pNN50: percentage of pairs of adjacent RR intervals differing by more than 50 ms; LF: Low frequency; HF: High frequency; SD1: Standard deviations of the distances from points to diagonal Y = X of the scattergram; SD2: Standard deviations of the distances from points to straight Y = -X+RRmean of the scattergram.

differences that between well-controlled HT and NT postmenopausal women in HRV.

The time effects in the majority of HRV parameters suggest that CET improved the cardiac autonomic control of both NT and HT postmenopausal women. Among these parameters, the RMSSD, pNN50, and SD1 are most affected by high-frequency variations in the HR and are frequently used as a marker of good cardiac vagal modulation[1]. Therefore, the improvement of these parameters suggests that CET increased the resting cardiac vagal modulation of postmenopausal women. These improvements are common physiological adaptations promoted by aerobic training, and an increase in parasympathetic parameters is frequently reported after a phase of training[30]. Improvements in RMSSD and SD1 as a result of CET were previously reported in NT postmenopausal women[12], corroborating with the results found. However, in accordance with our searches, the improvement in cardiac vagal modulation parameters with CET in HT postmenopausal women is shown for the first time and should be highlighted.

Time effects were reported for mean RR, SDNN, and SD2 too. These parameters are influenced by both low- and high-frequency variations of the HR, therefore, being associated as global parameters of cardiac autonomic control[1]. The positive effect of CET on the mean RR in NT postmenopausal women was shown previously[12]. These results suggest that, in addition to improvement on cardiac vagal modulation, CET may promote an improvement in the global cardiac autonomic modulation of postmenopausal women. In this population, improvements in autonomic control of the HR are relevant due to the increased risk of cardiovascular diseases associated with low autonomic control of the cardiovascular system[3-5,31]. Studies investigating the effects of CET on HRV in HT postmenopausal women are scarce, making it difficult to compare the results reported here. However, in HT middle-aged sedentary women, CET improved HRV[20]. In these women, the increase in global HRV is an important clinical effect due to the decreased cardiac autonomic modulation reported in this population[2,19], with up to 30% decrease in overall variability as measured by SDNN[4].

It is worth mentioning that these results reported in the present study refer to medicated HT postmenopausal women and intervention with combined exercise training with moderate intensity. Therefore, they cannot be generalized to women with untreated or uncontrolled hypertension, men, or exercises with other characteristics. Future studies with a similar design and the presence of a group without antihypertensive drugs could help us to explain the results found. As a possible limitation, we report that there is no group without exercise as an intervention, no control of antihypertensive drug classes and

doses, and the small sample size that could lead to type 2 error. Finally, we reiterate the importance of physical exercises after menopause regardless of the existence of hypertension, since, besides autonomic control alterations, they can generate improvements in blood pressure[23,32,33], lipid profile[15], endothelial function[34], oxidative profile[35], climacteric simptoms[36], and general cardiovascular health[33,37].

Conclusion

In summary, 10 weeks of combined exercise training improved the HRV parameters of both normotensive and hypertensive postmenopausal women without significant differences.

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ANEXO 3

NRC Research Press

ARTICLE

Isoflavone does not promote additional effects on heart rate variability of postmenopausal women performing combined exercise training: a clinical, controlled, randomized, double-blind study

Igor Moraes Mariano, Victor Hugo de Freitas, Juliene Gonçalves Costa Dechichi, Jaqueline Pontes Batista, Tállita Cristina Ferreira de Souza, Ana Luiza Amaral, Mateus de Lima Rodrigues, Victor Hugo Vilarinho Carrijo, and Guilherme Morais Puga

Abstract: The aim of the study was to investigate the effects of ingesting isoflavones associated with combined aerobic and resistance exercise training on heart rate variability (HRV) indices in postmenopausal women. Twenty-eight healthy postmenopausal women performed 10 weeks of combined exercise training associated with isoflavone (n = 16) or placebo (n = 12) supplementation. The RR intervals (RRi) were collected for 20 min using a heart rate monitor. Analysis of HRV was performed in time (mean squared difference of successive RRi (RMSSD), standard deviation of all normal RRi (SDNN), and percentage of adjacent RRi differing by more than 50 ms (pNN50)), frequency (low-frequency percentage (LF%), high-frequency percentage (HF%), and low-/high-frequency ratio (LF/HF)), and nonlinear domains (standard deviation of the instantaneous variability of the beat-to-beat interval (SD1), long-term variability of the continuous RRi (SD2), and their ratio (SD2/SD1)). Student's t test did not show differences between groups in any general baseline characteristic variables. The results of the generalized estimating equation tests did not demonstrate interaction or group effects for any HRV indices. However, the results reported time effects for mean RR ($p < 0.001$), RMSSD ($p = 0.044$), and SD1 ($p = 0.044$), with increases in these indices in response to exercise training. There were no time effects for LF%, HF%, LF/HF, SDNN, pNN50, SD2, or SD2/SD1. In conclusion, isoflavone supplementation did not promote additional effects on HRV indices of postmenopausal women subjected to 10 weeks of combined exercise training.

Novelty

- Combined training improves heart rate variability in postmenopausal women.
- Isoflavone supplementation did not promote additional effects on heart rate variability in postmenopausal women.

Key words: exercise, autonomic, supplementation, climacteric, isoflavones, aerobic, resistance, combined, menopause, heart rate variability.

Résumé : Le but de l'étude est d'étudier les effets de la consommation d'isoflavones associées à l'entraînement combiné d'exercices d'aérobie et de résistance sur les indices de variabilité de la fréquence cardiaque (« HRV ») chez les femmes postménopausées. Vingt-huit femmes postménopausées en bonne santé se soumettent à 10 semaines d'exercices combinés associés à une supplémentation en isoflavones (n = 16) ou à un placebo (n = 12). Les intervalles RR (« RRi ») sont collectés pendant 20 min à l'aide d'un moniteur de fréquence cardiaque. L'analyse HRV est effectuée dans les domaines temporel (différence quadratique moyenne des RRi successifs (« RMSSD »), écart type de tous les intervalles normaux (« SDNN ») et pourcentage d'intervalles adjacents différant de plus de 50 ms (« pNN50 »), fréquentiel (pourcentage de basse fréquence (« LF % »), de haute fréquence (« HF % ») et le ratio basse fréquence/haute fréquence (« LF/HF ») et non linéaire (écart type de la variabilité instantanée de l'intervalle battement à battement (« SD1 »), variabilité à long terme des intervalles continus (« SD2 ») et leur ratio (« SD2/SD1 »). À propos des caractéristiques initiales, le test t de Student ne révèle pas de différence entre les groupes. Les résultats des tests d'équation d'estimation généralisée ne démontrent aucun effet d'interaction ou de groupe pour aucun indice HRV. Cependant, les résultats présentent des effets temporels pour RR moyen ($p < 0{,}001$), RMSSD ($p = 0{,}044$) et SD1 ($p = 0{,}044$) et une augmentation de ces indices en réponse à l'entraînement physique. Il n'y a aucun effet temporel concernant LF %, HF %, LF/HF, SDNN, pNN50, SD2 et SD2/SD1. En conclusion, la supplémentation en isoflavones ne favorise pas d'effets additionnels sur les indices HRV des femmes postménopausées soumises à 10 semaines d'exercices combinés. [Traduit par la Rédaction]

Les nouveautés

- L'entraînement combiné améliore la variabilité de la fréquence cardiaque chez les femmes postménopausées.
- La supplémentation en isoflavones ne favorise pas d'effets additionnels sur la variabilité de la fréquence cardiaque chez les femmes postménopausées.

Mots-clés : exercice, autonome, supplémentation, climatère, isoflavones, aérobie, résistance, combiné, ménopause, variabilité de la fréquence cardiaque.

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Introduction

The inclusion of aerobic and resistance exercises in training programs has been recommended to maintain and improve the health and function of the cardiovascular system and skeletal muscles of young and older adults (Chodzko-Zajko et al. 2009; Garber et al. 2011). In postmenopausal women, combined exercise training (CET; aerobic and resistance exercises in the same session) may promote additional effects, which attenuates climacteric symptoms, systemic inflammation markers, and oxidative stress and improves bone health (Mendoza et al. 2016; Giolo et al. 2018). Furthermore, training programs that contain aerobic exercises may improve the heart rate variability (HRV) (i.e., a validated measure for evaluating cardiac autonomic modulation (Malik et al. 1996; Sandercock et al. 2005)) in postmenopausal women (Jurca et al. 2004; Sandercock et al. 2005).This improvement in HRV is an important effect as the reduced level of estrogen reported postmenopause may reduce cardiac modulation by the autonomic nervous system (Brockbank et al. 2000; Mercuro et al. 2000; Neves et al. 2007), which is associated with an increased risk of arrhythmia and sudden cardiac death (Malik et al. 1996; Mercuro et al. 2000).

Although the effect of therapy with female sex hormones on HRV remains controversial (Fernandes et al. 2005; Kiselev et al. 2018), there is evidence reporting the role of estrogen in the modulation of the autonomic nervous system (Mercuro et al. 1999, 2000; Saleh and Connell 2007). Indirect and direct mechanisms may be involved in this modulation (Mercuro et al. 2000; Saleh and Connell 2007; Lee et al. 2011). Postmenopausal symptoms such as hot flashes and sleep problems, for example, are associated with altered autonomic control of the heart rate (Lee et al. 2011). Previous studies (Thurston et al. 2010; de Zambotti et al. 2013) show significant decreases in cardiac vagal control during hot flashes in late perimenopausal and postmenopausal women. Furthermore, postmenopausal women exhibited higher basal levels of noradrenaline than premenopausal women (Mercuro et al. 1999). As a direct mechanism, estrogen may act within central nuclei to modulate autonomic function (Saleh and Connell 2007), showing a central mediated action of estrogen. In this way, isoflavone has been used as an alternative treatment aiming to reduce postmenopausal symptoms (Glazier and Bowman 2001; Carbonel et al. 2018). Isoflavone is a phytoestrogen that exhibits a similar chemical structure to estrogen, presenting high affinity to estrogen receptors (Carbonel et al. 2018). This leads us to suggest that isoflavone consumption could provide additional beneficial effects on HRV indices increased by exercise practice. However, understanding of the effects of isoflavone on HRV is limited and it is important to investigate whether isoflavone provides additive effects on HRV in postmenopausal women submitted to CET.

The aim of the present study was to investigate the effects of ingesting isoflavone in addition to CET on HRV indices in nonobese postmenopausal women. The hypothesis raised was that isoflavone would promote additional improvement in HRV indices compared with isolated CET.

Materials and methods

Participants

A total of 260 postmenopausal women (amenorrhea for at least 12 months) aged 50–70 years were recruited through advertisements in traditional (newspapers, radio, and television) and electronic media (social media), with the provision of a telephone contact for those who were interested. After contact, interviews were scheduled to verify compliance with the following inclusion criteria: able to engage in treadmill and resistance training; no history of cardiovascular disease, diabetes, renal pathologies, or hypertension; nonsmoker; no hormone therapy or isoflavones use for at least 3 years; and signed a consent form. The exclusion criteria were not taking all capsules, not performing the initial or final evaluations, or initiating another exercise protocol concomitant to the study. All volunteers were instructed to maintain their diet and sleep habits throughout the study. The follow-up flowchart is presented in Fig. 1. In total, 36 women who met the inclusion criteria were recruited and allocated (17 on placebo and exercise and 19 on isoflavone supplementation and exercise); of these, 32 completed the protocol and 4 were excluded from the HRV analyses because of bad signal quality, totaling 28 volunteers (12 on placebo and exercise and 16 on isoflavone supplementation and exercise). The sample and interventions used in the present study were the same as those used in a previous study aimed at verifying the effects of CET and isoflavone supplementation on climacteric symptoms in postmenopausal women (Costa et al. 2017). This study was approved by the local ethics committee (Federal University of Uberlândia; CAAE: 40622414.9.0000.5152) and recorded in the international registration of clinical trials at clinicaltrials.gov (identifier no. NCT03008785).

Study design

This study is a parallel randomized, double-blinded, placebo-controlled clinical trial. Initially, 38 possible samples (in accordance with the sample size calculation and estimated sample loss) were randomly assigned (by electronic software) to the PLA group (n = 19) who received placebo and to the ISO group (n = 19) who received isoflavone supplementation. However, after recruitment, only 36 women met the inclusion criteria and were allocated to the PLA group (n = 17) and the ISO group (n = 19). In association with placebo or isoflavone consumption, participants performed 30 sessions of CET for 10 weeks. Before the first day of training, participants were characterized by anthropometric evaluation and a questionnaire on physical activity level. Furthermore, they performed a treadmill incremental test and a maximal strength test (1 repetition maximum test; 1RM), with an interval of at least 48 h, to determine the intensity of training. HRV was evaluated before and after training, after at least 48 h without exercise. Volunteers were instructed to abstain from alcohol and caffeine. All procedures were performed in the Cardiorespiratory and Metabolic Physiology Laboratory of the Faculty of Physical Education at the Federal University of Uberlândia from February to December 2015.

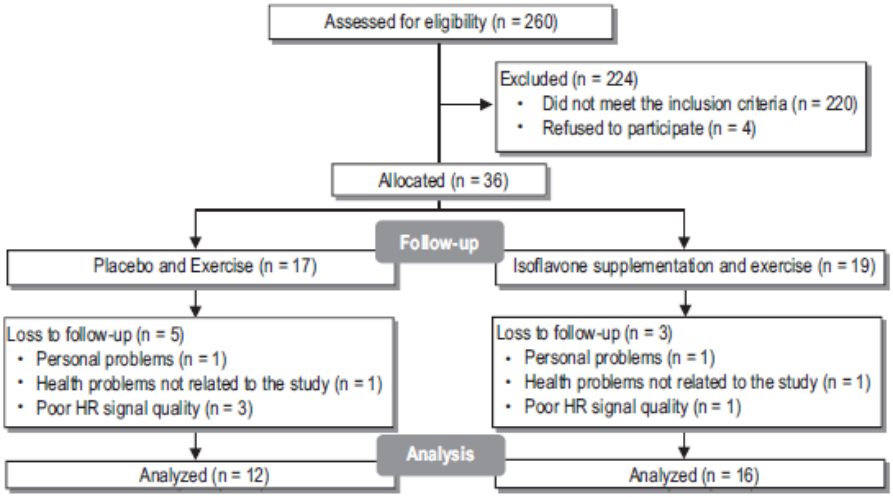
Anthropometric measurements and physical activity level

The anthropometric evaluations were performed in an isolated environment in the morning after 8 h of fasting. The following variables were measured: body mass, using an electronic scale (Filizola, São Paulo, SP, Brazil); height, using a fixed stadiometer (Sanny, São Bernardo do Campo, SP, Brazil); abdominal, waist, and hip circumferences, using a 0.5-cm wide inelastic tape (Filizola); and fat mass, using tetrapolar bioimpedance (Biodynamics Model 450c; Biodynamics, Shoreline, Wash., USA). Physical activity level was assessed using the International Physical Activity Questionnaire (IPAQ; Short Version), validated for the Brazilian population (Matsudo et al. 2001).

Incremental treadmill test

The submaximal incremental treadmill test was performed with a fixed velocity of 5.5 km/h and intensity imposed by the incline (%) to identify exercise intensity between ventilatory thresholds 1 and 2 for exercise prescription. After a 5-min warm-up with a 0% incline, the test began with a 1% incline. The protocol consisted of 2-min stages with 1% increments in incline per stage until the volunteers reached 85% of their predicted maximum heart rate or 18 for the rate of perceived exertion (Borg 1982). Oxygen uptake and carbon dioxide output were recorded during the tests using a gas analyzer (Cosmed Quark CPET, Rome, Italy) to identify the ventilatory thresholds based on ventilatory equivalents (Wasserman 1984).

Fig. 1. Follow-up flowchart. HR, heart rate.



1RM test

For the 1RM test, participants performed a specific warm-up consisting of the same exercise as the test, with 2 sets at intensities of around 40%–50% and 60%–80% of the subjective estimate of 1RM and with 8–10 and 3–5 repetitions, respectively. After this warm-up, a maximum of 5 attempts were allowed per exercise to find the highest workload at which the participant could only perform 1 complete movement with the correct technique (Maud and Foster 2006). If the 1RM score was not found in the first session, a new session was scheduled after an interval of at least 48 h. The order of exercises tested was leg press, bench press, lateral pulldown, pec deck, and seated cable row.

Combined exercise training program

The training program consisted of combined aerobic and resistance exercises performed 3 times a week in 45-min sessions for 10 weeks. The sessions began with a 5-min warm-up on a treadmill at 5.5 km/h without inclination, followed by 20 min of aerobic exercises and 20 min of resistance exercises. The aerobic training was performed at a velocity of 5.5 km/h with the treadmill inclination corresponding to between ventilatory thresholds 1 and 2 determined in an incremental treadmill test. Intensity increments of 20% were performed in the fifth week of training. Data on volunteers who were absent for more than 15% of training were excluded from the analysis.

The resistance exercises were performed in 2 sets of 15 repetitions, with 30 s between exercises and sets. Seven resistance exercises were performed: leg press 45° (hip and knee extension); chest press in vertical machine (shoulder horizontal abduction and elbow extension); anterior latissimus dorsi pulldown (shoulder abduction and elbow flexion); seated cable row (shoulder extension and elbow flexion); pec deck (shoulder horizontal adduction with flexed elbows); squat with lumbar Swiss ball support (hip and knee extension); and classic abdominal crunch (spine flexion with fixed hip and flexed knee on a flat surface). The resistance exercise intensity corresponded to 60% of 1RM. A new 1RM test was carried out in the fifth week of training for load readjustment.

Heart rate analysis

RR intervals (RRi) were collected for 20 min in a seated position, with spontaneous breathing, in a well-lit room using a heart rate monitor (Polar RS800cx, Polar Electro Oy, Kempele, Finland; sampling frequency, 1000 Hz) and without the influence of sensorial stimuli. Heart rate data were transferred to a computer using Polar Pro trainer5 software (Polar Electro Oy), after which the RRi were visually inspected and artifacts were replaced by the mean of the adjacent values. Samples were selected from the range of 300 s with the fewest artifacts closest to the time series end, and signals with more than 2% of artifacts were discarded (Malik et al. 1996). HRV analyses were performed in time, frequency, and nonlinear domains (Malik et al. 1996) using validated (Tarvainen et al. 2014) software (Kubios HRV 3.0.0; University of Kuopio, Kuopio, Finland).

The analyzed time-domain indices included the square root of the mean squared difference of successive RRi (RMSSD), the standard deviation of all normal RRi (SDNN), and the percentage of adjacent RRi differing by more than 50 ms (pNN50). For frequency-domain analysis, time series were interpolated at 4 Hz and the linear trend component signal was removed using the smooth prior technique. Next, the signal was multiplied by the Hanning window and a fast Fourier transform of the product was calculated. Thus, spectral bands were calculated through the integral of the power spectral density curve and specified in low (LF: 0.04–0.15 Hz) and high frequencies (HF: 0.15–0.4 Hz), as well as the ratio (LF/HF). Both LF and HF were normalized (percentage of LF (LF%) and HF (HF%), respectively), representing the relative contribution of each component to the total power minus the very-low-frequency component. For nonlinear indices the Poincaré plot was analyzed, and the standard deviation of the instantaneous variability of the beat-to-beat interval (SD1) and the long-term variability of the continuous RRi (SD2) were analyzed, along with the ratio (SD2/SD1).

Supplementation

Volunteers took a capsule of isoflavone or placebo every day of the week (including weekends) from the first day to the last day of training, totaling 70 capsules per volunteer during the 10 weeks of training. Every Monday, each volunteer received a plastic refill containing the substances (isoflavone or placebo) with markings for the days. In the initial and final evaluations, volunteers did not receive supplementation. At every training session, participants were reminded and encouraged to maintain supplementation. The ISO capsules contained 100 mg of isoflavone (composition: 3.3% genistein, 93.5% daidzein, and 3.2% glycitein) that was de-

Table 1. Heart rate variability.

Groups	Pre-intervention	Post-intervention	Δ (95% CI)	*p* Group	*p* Time	*p* Inter.
Mean RR, ms						
ISO	844.8±84.8	885.4±139.7	40.6 (–7.2 to 88.5)	0.125	<0.001	0.113
PLA	760.1±104.5	855.3±114.2	95.2 (47.6 to 142.8)			
SDNN, ms						
ISO	25.3±11.0	25.9±10.4	0.6 (–8.1 to 9.4)	0.934	0.172	0.235
PLA	21.0±14.3	29.7±17.2	8.7 (–1.4 to 18.8)			
RMSSD, ms						
ISO	19.5±10.9	23.1±15.2	3.6 (–5.2 to 12.5)	0.883	0.044	0.338
PLA	15.6±11.4	25.9±14.9	10.2 (0.1 to 20.4)			
pNN50, %						
ISO	4.1±7.4	8.0±15.7	3.9 (–3.4 to 11.3)	0.779	0.094	0.769
PLA	2.4±6.7	8.1±10.5	5.6 (–2.8 to 14.0)			
LF%, n.u.						
ISO	74.3±13.6	71.9±22.2	–2.3 (–13.6 to 8.9)	0.574	0.339	0.672
PLA	73.7±9.5	67.6±18.2	–6.0 (–19.1 to 6.9)			
HF%, n.u.						
ISO	25.7±13.6	28.0±22.2	2.3 (–8.9 to 13.6)	0.578	0.342	0.674
PLA	26.3±9.5	32.3±18.1	6.0 (–7.0 to 19.0)			
LF/HF						
ISO	4.2±2.9	5.1±5.7	0.9 (–1.5 to 3.4)	0.156	0.760	0.522
PLA	3.4±1.9	3.1±2.1	–0.3 (–3.2 to 2.5)			
SD1, ms						
ISO	13.8±7.7	16.4±10.8	2.6 (–3.7 to 8.8)	0.883	0.044	0.337
PLA	11.1±8.1	18.4±10.5	7.3 (0.1 to 14.5)			
SD2, ms						
ISO	32.8±14.0	32.0±12.1	–0.7 (–11.9 to 10.5)	0.994	0.295	0.224
PLA	27.4±18.8	37.3±22.7	9.9 (–3.1 to 22.8)			
SD2/SD1						
ISO	2.6±0.8	2.4±0.9	–0.2 (–0.7 to 0.3)	0.322	0.311	0.843
PLA	2.4±0.6	2.2±0.8	–0.2 (–0.7 to 0.4)			

Note: Values are presented as means ± SD and Δ (95% CI). CI, confidence interval; HF%, high-frequency percentage; inter., interaction; ISO, isoflavone group; LF%, low-frequency percentage; LF/HF, low-/high-frequency ratio; n.u., normalized units; PLA, placebo group; pNN50, percentage of pairs of adjacent RR intervals differing by more than 50 ms; RMSSD, root mean square of the successive differences of RR intervals; SD1, standard deviations of the distances from points to diagonal $Y = X$ of the scattergram; SD2, standard deviations of the distances from points to straight $Y = -X + RRmean$ of the scattergram; SDNN, standard deviation of normal RR intervals.

rived from soybean, corresponding to approximately 37.58 g of soy (Wang and Murphy 1994), whereas the PLA capsules contained 100 mg of cornstarch. All capsules were identical in appearance, taste, and smell.

Statistical analysis

The sample calculation was performed using G*Power software (version 3.1.9.2; Faul et al. 2009) and considering RMSSD as the main variable. An a priori *f* family test for within–between interaction repeated-measures ANOVA was performed, with a possible effect size (*f*) of 0.3, a probability of error α of 0.05, power (1-β) of 0.8, correlation between repeated measures of 0.5, and a nonsphericity correction of 1. Thus, a total sample size (summed of over all groups) of 24 individuals was determined.

The pre- and post-HRV results are presented as means ± SD, variation (Δ), and lower and upper limits of the 95% confidence interval. Normality of data was tested using the Shapiro–Wilk test. Student's *t* test was used to compare HRV and the general characteristics of participants at the pre-intervention phase, and data are presented as means ± SD. The Mann–Whitney test was performed for variables without normal distribution, and these data are presented as median and interquartile range (25%–75%). Pearson's χ^2 test was used to compare the physical activity level (by IPAQ) between groups, followed by the Monte Carlo test when the expected frequency was less than 5. A 2-factor (time and group) generalized estimating equation technique was performed for between, within, and interaction comparisons. All analyses were performed using IBM SPSS Statistics 21 (IBM Corp., Armonk, N.Y., USA). The significance level adopted was $p < 0.05$.

Results

The IPAQ analyses (data not shown) demonstrated that although no participants practiced regular exercises, none of the women were sedentary. The levels of physical activity were not different between groups ($\chi^2 = 0.609$; $p = 0.772$). No differences were found between groups at any pre-intervention HRV index (values can be checked in Table 1; statistical data not shown). However, there was a significant difference in mean RR values ($p = 0.026$). The general baseline characteristics are presented in Table 2. There were no differences between groups in any general baseline characteristic variables.

Table 1 presents the HRV data. The results of the generalized estimating equation tests did not show interaction or group effects for any HRV indices. However, the results reported time effects for mean RR, RMSSD, and SD1, with an increase in these indices in response to CET. There were no differences between moments for LF%, HF%, LF/HF, SDNN, pNN50, SD2, or SD2/SD1.

Discussion

The present study aimed to investigate if isoflavone promoted additional benefits to HRV indices over those provided by CET in postmenopausal women. Our hypothesis was based on similarity of chemical structure between isoflavone and estrogen and its high affinity to estrogen receptors (Carbonel et al. 2018). When

Table 2. General baseline characteristics.

Variable	PLA, $n = 12$	ISO, $n = 16$	p
Age, y	52.6±5.3	56.1±5.5	0.100
Time after menopause, y	3.0 (1.4–5.8)	4.5 (2.0–12.0)	0.217
Body mass, kg	63.2±7.5	65.9±8.8	0.413
Height, m	1.55±0.05	1.58±0.05	0.830
Body mass index, kg/m²	27.1±2.6	26.4±3.4	0.555
Abdominal circumference, cm	90.3 (87.3–96.8)	100.5 (84.5–104.3)	0.763
Waist circumference, cm	81.0 (76.0–86.3)	82.3 (74.7–91.5)	0.561
Hip circumference, cm	102.3±6.8	103.7±7.3	0.614
Waist/hip ratio	0.79±0.06	0.78±0.06	0.648
Leg press 1RM, kg	169.6±32.4	158.2±41.6	0.439
Bench press 1RM, kg	27.3±4.2	25.0±5.2	0.230
Lat pulldown 1RM, kg	30.0 (25.0–35.0)	30.0 (30.0–33.8)	0.807
Pec deck 1RM, kg	19.2±5.1	19.5±4.4	0.855
Seated cable row 1RM, kg	57.1±8.4	56.6±12.1	0.899

Note: Data are presented as means ± SD in variables with normal distribution (p from Students t test) and median with interquartile range (25%–75%) in variables without normal distribution (p from Mann–Whitney test). 1RM, 1-repetition maximum test; ISO, isoflavone group; PLA, placebo group.

stimulated, estrogen receptors may directly (i.e., acting within central nuclei) or indirectly (i.e., regulation of hot flashes and sleep problems; change in basal level of noradrenaline) modulate autonomic function (Mercuro et al. 1999, 2000; Saleh and Connell 2007; Lee et al. 2011). However, the results refuted the hypothesis raised, as only time effects were found, in accordance with studies that did not find any benefits of female sex hormonal therapy on cardiac autonomic modulation (Fernandes et al. 2005; Kiselev et al. 2018).

Postmenopausal symptoms (such as hot flashes and sleep problems) associated with reduced levels of estrogen are related to decreased autonomic control of the heart rate (Lee et al. 2011). A systematic review and meta-analysis of randomized controlled trials concluded that soy isoflavone supplements are significantly more effective than placebo in reducing the frequency and severity of hot flashes (Taku et al. 2012). Therefore, it was speculated that isoflavone supplementation could promote an additive reduction in postmenopausal symptoms occasioned by exercise practices (Ivarsson et al. 1998; Costa et al. 2017), and consequently promote an indirect additional effect on HRV. Although hot flashes and sleep disturbance symptoms were not analyzed in the present study, a previous study showed that isoflavone supplementation did not promote additive effects in improving these climacteric symptoms when ingested concomitantly with 10 weeks of CET (Costa et al. 2017). Therefore, the speculation made in the present study was not confirmed.

Another hypothesis was that isoflavone could interact with estrogen receptors in central nuclei to modulate autonomic function (Saleh and Connell 2007), promoting additive improvement in HRV promoted by CET. Modulation in central areas in response to exercise (Michelini and Stern 2009; Martins-Pinge 2011), which reduces the response efficiency of isoflavone, may explain the lack of additive effect found in the present study. Furthermore, β-endorphin released during exercise can stabilize thermoregulation and prevent hot flashes (Ivarsson et al. 1998). Up to now, no additive effect of isoflavone combined with CET on HRV has been found (Costa et al. 2017).

The time effects reported in mean RR, RMSSD, and SD1 suggest that CET increased the resting cardiac autonomic modulation of postmenopausal women. Mean RR is suggested as a global parameter of cardiac autonomic control (Malik et al. 1996). On the other hand, RMSSD and SD1 are most affected by high-frequency variations in the heart rate, and are used as a marker of cardiac vagal control (Malik et al. 1996). Improvement in global or vagal indices of autonomic control of the heart rate in postmenopausal women is an important result due to the elevated risk of cardiovascular disease in this population (Kuo et al. 1999; Brockbank et al. 2000; Neves et al. 2007; Pathak et al. 2017). These results suggest that CET promoted intrinsic and/or central cardiovascular adaptations (Michelini and Stern 2009; Martins-Pinge 2011), which is in accordance with the supposition made in previous paragraphs.

The lack of a group with only isoflavone supplementation, a group without CET, and evaluation of the amount of isoflavone that appears in the blood could be some limitations of this study. However, as the aim of the current study was to investigate if isoflavone supplementation could have additive effects on the exercise-derived responses in HRV, we believe that our study could help to answer this question. Further studies are needed to investigate other doses of isoflavone and the association of this supplementation with other kinds of exercises.

The class of isoflavone used in the present study may be another limitation. The 3 primary isoflavones found in soy are genistein, daidzein, and glycitein (Murphy et al. 1999). Apparently, studies that show effects of isoflavone on climacteric symptoms use compounds containing at least 15 mg of genistein (Scambia et al. 2000; Williamson-Hughes et al. 2006), which is a larger quantity than that used in the present study (3.3 mg). A previous study that used a similar quantity of isoflavone compounds also did not show additive effects on a reduction in climacteric symptoms promoted by CET (Costa et al. 2017). However, to date, no studies have investigated the effects of different classes of isoflavone on HRV modulation.

In summary, isoflavone did not promote additional effects on HRV indices of postmenopausal women submitted to 10 weeks of CET. The study was conducted in generally healthy, nonobese women; therefore, the results might not be applicable to other groups receiving treatment with higher potency medication or for longer than 10 weeks. It is also important to note that this result is applicable only for isoflavone supplementation and may not be extrapolated to isoflavone consumption from natural and regular foods.

Conflict of interest statement

All authors declare no conflicts of interest.

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