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THARCIANO LUIZ TEIXEIRA BRAGA DA SILVA

EFEITOS DO EXERCÍCIO FÍSICO RESISTIDO SOBRE A FUNÇÃO VASCULAR E PRESSÃO ARTERIAL EM RATOS: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

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Tese apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Sergipe como requisito parcial à obtenção do grau de Doutor em Ciências da Saúde.

Orientador: Prof. Dr. Márcio Roberto V. Santos

Co-orientador: Prof. Dr. Leonardo R. Bonjardim

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Aprovada em 06/03/2015

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Orientador: Prof. Dr. Márcio Roberto V. Santos.
Universidade Federal de Sergipe – DFS/UFS

____

1º Examinador: Prof. Dr. Paulo Ricardo Saquete M. Filho.
Universidade Federal de Sergipe – DESL/UFS

____

2º Examinador: Prof. Dr. Vitor Oliveira Carvalho.
Universidade Federal de Sergipe – DFT/UFS

____

3º Examinador: Prof. Dr. Eduardo Seixas Prado.
Universidade Federal de Alagoas – DEF/UFAL.

____

4º Examinador: Prof. Dr. Marcelo Mendonça Mota.
Faculdade Estácio de Sergipe – DEF/FASE/ESTÁCIO DE SÁ.

PARECER

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"Determinação, coragem e autoconfiança são fatores decisivos para o sucesso. Não importam quais sejam os obstáculos e as dificuldades. Se estamos possuídos de uma inabalável determinação, conseguiremos superá-los. Independentemente das circunstâncias, devemos ser sempre humildes, recatados e despidos de orgulho."

Dalai Lama.

SILVA, T.L.T.B. **EFEITOS DO EXERCÍCIO FÍSICO RESISTIDO SOBRE A FUNÇÃO VASCULAR EM RATOS: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE.** 2015. 80p. Tese (Doutorado em Ciências da Saúde) – Universidade Federal de Sergipe, Aracaju.

RESUMO

Meta-análises com estudos pré-clínicos são relativamente novas e promovem diretrizes para os estudos clínicos. A literatura demonstra que os efeitos do exercício resistido sobre o sistema cardiovascular em modelos experimentais ainda são controversos. O objetivo desta meta-análise foi avaliar os efeitos do exercício resistido sobre a função vascular e pressão arterial em ratos. Foram investigados diferentes bancos de dados buscando estudos que avaliaram os efeitos do exercício resistido sobre a sensibilidade vascular, resposta máxima e pressão arterial em ratos até 30 de Setembro de 2014. Após a seleção dos estudos, os dados foram agrupados pelo método de variância inversa genérico usando o modelo de efeitos aleatórios e expressa como a diferença da média padronizada, Hedges g e intervalos de confiança de 95% (IC 95%). Treze estudos foram incluídos. Nossa meta-análise demonstrou que o exercício resistido em ratos não altera a sensibilidade vascular, mas promove o aumento do relaxamento vascular ($P<0,01$). Além disso, observou-se uma redução da pressão arterial nos animais exercitados ($p<0,01$). As análises de subgrupo demonstraram que o exercício de agachamento ($p<0,01$), com baixos volumes de exercício resistido ($p<0,05$) e com intensidade moderada/alta ($p<0,001$) reduz a pressão arterial. Os resultados desta meta-análise sugerem que o exercício resistido melhora a função vascular e diminui a pressão arterial em ratos. No entanto, mais estudos são necessários para entender melhor os efeitos de diferentes protocolos de exercícios resistidos sobre o sistema cardiovascular.

Palavras-Chave: Meta-análise; Exercício resistido; Pressão arterial.

SILVA, T.L.T.B. **EFFECTS OF RESISTANCE EXERCISE ON VASCULAR FUNCTION AND BLOOD PRESSURE IN RATS: A SYSTEMATIC REVIEW AND META-ANALYSIS.** 2015. 80p. Tese (Doutorado em Ciências da Saúde) – Universidade Federal de Sergipe, Aracaju.

ABSTRACT

Meta-analyses with preclinical studies are relatively new and promote guidelines for clinical studies. The literature has showed that the effects of resistance exercise on the cardiovascular system in experimental models are still controversy. The aim of this meta-analysis was to evaluate the effects of resistance exercise on vascular function and blood pressure in rats. Different databases were searched for studies evaluating the effects of resistance exercise on vascular sensitivity, maximal response and blood pressure in rats up to September 30, 2014. Post intervention between-group effect sizes were pooled with the generic inverse variance method using random-effect model and expressed as standardized mean difference, Hedges g, with 95% confidence intervals (95% CI). Thirteen eligible studies were included. Our meta-analysis showed that resistance exercise in rats does not alter the vascular sensitivity, but promotes increased vascular relaxation ($p<0.01$). In addition, we observed a reduction in blood pressure in the exercised animals ($p<0.01$). Subgroup analysis showed that squat exercise ($p<0.01$), with low volumes of resistance exercise ($p<0.05$) and with moderate/high intensity ($p<0.001$) reduces the blood pressure. The results of this meta-analysis suggests that resistance exercise improves the vascular function and decreases the blood pressure in rats. However, further studies are needed to better understand the effects of different resistance exercise protocols on the cardiovascular system.

Keywords: Meta-analysis; Resistance exercise; Arterial pressure.

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LISTA DE ABREVIATURAS

1 RM- Uma repetição máxima

IC 95%- Intervalo de confiança de 95%

DP- Desvio padrão

E.P.M- Erro padrão da média

PAM- Pressão arterial média

PAS- Pressão arterial sistólica

PAD- Pressão arterial diastólica

pD_2 – Quantidade da droga necessária para produzir 50% da Rmax (estima a sensibilidade)

Rmax- Resposta máxima ao agente vasoativo

SMD- Diferença da média ponderada

SUMÁRIO

1. INTRODUÇÃO

O exercício físico aeróbio é caracterizado pela realização de movimentos cíclicos (metabolismo aeróbio) que demonstram provocar importantes alterações autonômicas e hemodinâmicas (HOWLEY, 2001; KURU et al., 2002; FAGARD, 2006; MCALLISTER et al., 2008). Por outro lado, o exercício físico resistido ou exercício resistido possui um metabolismo energético prioritariamente anaeróbio e caracteriza-se pela execução de movimentos intermitentes em que os músculos de um segmento específico do corpo estão contraídos contra uma força que se opõe ao movimento (HOWLEY, 2001).

Os relatos sobre os efeitos do exercício aeróbio na redução da pressão arterial e na melhora da função vascular já está consolidado na literatura (KELLEY; KELLEY; TRAN, 2001; SASAKI; DOS SANTOS, 2006; RICHTER et al., 2010; DIMEO et al., 2012; PAL; RADAVELLI-BAGATINI; HO, 2013). Diretrizes nacionais e internacionais sobre o controle e o tratamento das doenças cardiovasculares indicam a associação do exercício aeróbio ao resistido como uma eficiente terapia não medicamentosa (MEKA et al., 2008; VI DBH et al., 2010; ACHTTIEN et al., 2013; ACHTTIEN et al., 2015).

Devido a maior quantidade de estudos pré-clínicos com o exercício aeróbio as revisões sistemáticas têm sido desenvolvidas com frequência e servem de parâmetro para a realização de novos estudos (JASPERSE; LAUGHLIN, 2008; BEZERRA et al., 2012; AUSTIN et al., 2014; PLOUGHMAN et al., 2015). Apesar disso, até o presente momento foi encontrada na literatura científica somente uma revisão sistemática com meta-análise que demonstra os benefícios do exercício aeróbio em ratos que foram induzidos ao acidente vascular cerebral (SCHMIDT et al., 2014). De uma forma geral, a literatura indica que as revisões sistemáticas com ou sem meta-análise são uma nova prática de pesquisa na área que envolve os efeitos do exercício físico e a ciência básica.

Estudos pré-clínicos que objetivam avaliar os mecanismos envolvidos nos efeitos do exercício resistido sobre os parâmetros cardiovasculares na saúde e na doença são observados com certa frequência (BARAUNA et al., 2005; BARAUNA et al., 2008; DE CÁSSIA et al., 2008; ARAUJO et al., 2013; DAS NEVES et al., 2013; FONTES et al., 2014; GRANS et al., 2014; MOTA et al., 2014). Atualmente, são descritos diversos modelos de exercício resistido para ratos e diferentes protocolos de treinamento (CHOLEWA et al., 2014).

Os dois modelos mais utilizados para avaliar os efeitos cardiovasculares do exercício resistido nas ciências básicas é o modelo de agachamento para ratos e o exercício de subida em escadas (TAMAKI; UCHIYAMA; NAKANO, 1992; LEE et al., 2004). O primeiro estudo pré-clínico que demonstrou as adaptações cardiovasculares provenientes do exercício resistido em ratos foi desenvolvido por BARAUNA et al., 2005. Isto indica que o exercício resistido em ratos também é uma prática relativamente nova na ciência básica e pode ser uma importante ferramenta para a descoberta de novos mecanismos que contribuam no controle das desordens cardiovasculares. Devido à grande divergência de protocolos, os efeitos do exercício resistido observados na literatura ainda são bastante controversos. É importante também destacar que as variáveis, intensidade, duração, frequência e intervalo de repouso, influenciam diretamente no efeito dose-resposta do exercício resistido (ASHOR et al., 2015).

Recentemente, o nosso grupo demonstrou a eficiência do exercício resistido em melhorar a função vascular e/ou reduzir a pressão arterial em ratos saudáveis, diabéticos e hipertensos (ARAUJO et al., 2013; FONTES et al., 2014; MOTA et al., 2014). Da mesma forma, já foi demonstrado que o exercício resistido pode tanto aumentar a função vascular após uma sessão de exercício, quanto reduzir a pressão arterial em ratos hipertensos (FARIA et al., 2010). Outros estudos também indicam que a redução da pressão arterial pode ocorrer em animais saudáveis após o exercício resistido crônico (BARAUNA et al., 2005; DE CÁSSIA et al., 2008). Por outro lado, também existem evidências conflitantes que não demonstram alterações na função vascular e na pressão arterial em ratos saudáveis submetidos ao exercício resistido (BARAUNA et al., 2008; HARRIS et al., 2010).

Recentemente, a publicação de um guia prático para a realização de meta-análises com dados provenientes dos estudos pré-clínicos tem facilitado a orientação para o desenvolvimento dos estudos meta-analíticos em modelos animais (VESTERINEN et al., 2014). Da mesma forma que os estudos de meta-análise podem orientar as decisões clínicas e de pesquisas em humanos, a elaboração de revisões sistemáticas com meta-análise de estudos pré-clínicos pode servir como parâmetro para um maior ajuste metodológico nos estudos em modelos animais. Com isso, podemos encurtar a distância da translação do conhecimento pré-clínico/clínico sobre os mecanismos das doenças.

Dentro deste contexto, foi elaborado um artigo que se encontra no capítulo de resultados da presente tese. Este artigo foi intitulado de "Effects of resistance exercise on vascular function and blood pressure in rats: a meta-analysis" e avaliou os efeitos do exercício resistido sobre a função vascular e a pressão arterial em ratos através de uma revisão sistemática com meta análise. O segundo artigo (suplementar/ Apêndice) que compõe esta tese, "Resistance exercise acutely enhances mesenteric artery insulin-induced relaxation in healthy rats", avaliou os efeitos agudos de uma sessão de exercício resistido sobre as ações vasculares da insulina em artéria mesentérica de ratos. O artigo suplementar (Apêndice B) desta tese foi o fator motivador para o desenvolvimento da presente meta-análise. A partir da elaboração do estudo anterior, observamos a grande variabilidade dos protocolos de exercícios resistidos para ratos, como também, a crescente publicação nesta área de pesquisa. Os resultados do artigo suplementar estão contidos nesta meta-análise.

2. HIPÓTESE

O exercício resistido aumenta a função vascular e reduz a pressão arterial em ratos.

3. OBJETIVO

Avaliar através de uma meta-análise os efeitos do exercício resistido sobre a função vascular e pressão arterial em ratos.

4. MATERIAL E MÉTODOS

4.1 Fundamentação da metodologia

A fundamentação metodológica para esta meta-análise teve como base o guia prático para a realização de meta-análises em estudos pré-clínicos elaborado recentemente por Vesterinen et al., 2014. Também foi utilizado para uma melhor elaboração dos métodos de pesquisa, meta-análises pré-clínicas previamente publicadas (VAN DRONGELEN et al. 2012; SCHMIDT et al., 2014).

4.2 Elaboração da pergunta do estudo

A estratégia **PICO** foi utilizada para a construção da pergunta deste estudo. **PICO** representa um acrônimo para **P**aciente (população), **I**ntervenção, **C**omparação (controle) e "**O**utcomes" (desfecho) (DE SANTOS; PIMENTA; NOBRE, 2007). Para a elaboração da pergunta do estudo partimos da ideia que as desordens cardiovasculares são combatidas com a intervenção multidisciplinar e o exercício físico pode ser uma importante ferramenta para auxiliar no tratamento de diversas doenças. Atualmente, diretrizes indicam a associação do exercício aeróbio ao resistido como uma terapia não medicamentosa para as desordens cardiovasculares (MEKA et al., 2008; VI DBH et al., 2010; ACHTTIEN et al., 2013; ACHTTIEN et al., 2015). Dentro deste contexto, elaboramos a seguinte pergunta para a presente revisão sistemática e meta-análise: “O exercício físico resistido é capaz de aumentar a função vascular e reduzir a pressão arterial em ratos?”

4.3 Estratégia de pesquisa

Nós pesquisamos nos bancos de dados do Pubmed/Medline, Bireme, Embase, Lilacs e Cochrane Controlled Trials Database em setembro de 2014 todos os estudos originais que avaliaram os efeitos do exercício resistido sobre a pressão arterial e a função vascular de ratos. A estratégia de pesquisa utilizada para obter resumos de estudos foi feita com as palavras-chave “*resistance exercise” and “rats*”. Foi realizada também uma busca manual e identificação através das listas de referências. As bibliografias dos artigos foram cruzadas para obter mais artigos.

4.4 Delineamento da pesquisa

Estudos pré-clínicos com ratos que foram submetidos ao exercício resistido e avaliaram os efeitos cardiovasculares. Para possibilitar um maior controle do viés de publicação foram adotadas as seguintes estratégias: utilização de número ampliado de bases de dados e rejeição de limites relacionados à data de publicação. Quanto ao idioma de publicação, optou-se por artigos escritos na língua inglesa.

4.5 Critérios de elegibilidade

Dois autores independentes verificaram os resumos obtidos nas pesquisas e os artigos considerados relevantes para este estudo tiveram a lista de referências analisadas para acessar novos artigos. Caso um dos pesquisadores entendesse que uma referência tinha potencial de elegibilidade o artigo completo era avaliado. Em todo o processo de análise dos artigos os dois autores discutiram as dúvidas e a decisão final de qualquer desacordo das partes era resolvida por consenso ou um terceiro pesquisador.

Somente foram considerados elegíveis para a inclusão deste estudo os artigos com a língua inglesa e que o exercício resistido se caracterizasse pela execução de movimentos intermitentes compostos de séries, repetições e intervalo de descanso. Foram também incluídos na meta-análise os estudos envolvendo ratos saudáveis ou com doenças crônicas que executaram o exercício resistido. Foram excluídos os estudos que envolvessem qualquer outro tipo de exercício e também animais de outra espécie.

4.6 Desfechos

Os nossos principais desfechos de interesse desta meta-análise foi à resposta relaxante arterial induzida por agentes vasoativos e a pressão arterial média. Caso o artigo não apresentasse os valores da pressão arterial média (PAM) as mesmas eram calculadas a partir das pressões arterial sistólica e diastólica (PAM= PAS + (PADx2)/3). Qualquer outra informação necessária foi solicitada por e-mail ao autor de correspondência do artigo original.

4.7 Extração dos dados

A extração dos dados foi feita por dois pesquisadores de cada estudo selecionado para a meta-análise. Foram registrados os dados considerando a espécie, o tamanho da amostra, os grupos do estudo, as características da amostra, a caracterização do protocolo de exercício, a duração da intervenção, técnicas de mensuração, os desfechos da pressão arterial e da função vascular. A função vascular foi representada pela sensibilidade vascular (pD_2 e/ou EC_{50}, concentração necessária para obter 50% do efeito máximo) e pela resposta máxima (Rmax, efeito máximo do agente vasoativo). A partir de cada resposta da pressão arterial média e da função vascular nós registramos o número de ratos e o desvio padrão ou erro padrão da média.

4.8 Avaliação da qualidade dos estudos incluídos

Até o presente momento, não foi descrito na literatura científica uma lista que quantifique a qualidade dos estudos pré-clínicos que avaliaram os efeitos do exercício resistido. Para avaliar a qualidade metodológica dos estudos incluídos nesta meta-análise, uma lista foi elaborada e avaliada por dois pesquisadores independentes. Está lista foi adaptada de Van Drongelen et al., 2012 e Schmidt et al., 2014. Desta forma, buscamos adaptar e modificar para avaliar a qualidade dos estudos incluídos, como também, minimizar o viés de publicação. Os itens de qualidade adotados são critérios metodológicos aceitos em estudos experimentais com exercício físico. Foi elaborada uma sistemática de pontuação (negativo ou positivo) para o *score*/percentual (%) dos itens obtidos nos estudos incluídos na amostra. Os estudos foram classificados em duas categorias de qualidade:

- Categoria I, 6-10 critérios, considerado estudo de alta qualidade;

- Categoria II, 0-5 critérios, considerado estudo de baixa qualidade.

Foram adotados os seguintes critérios (itens) de qualidade:

1) Randomização;

2) Cumprimento dos regulamentos de bem-estar animal;

3) Idade e/ou peso do animal;

4) Número claro de animais utilizados para o estudo;

5) Drogas e reagentes descritos na metodologia (fabricante);

6) Respostas fisiológicas ≥ que 5 medições por experimento;

7) Verificação de parâmetros fisiológicos (temperatura, pressão arterial, reatividade vascular, sangue perfil bioquímico, morfologia, função cardíaca);

8) Protocolo de exercício descrito na metodologia;

9) Familiarização do animal com o protocolo de treinamento;

10) Teste de uma repetição máxima (1 RM) ou carga máxima.

4.9 Análise estatística

Os dados foram agrupados pelo método de variância inversa genérico usando o modelo de efeitos aleatórios e expressa como as diferenças das médias ponderadas (SMD), Hedges *g*, com intervalo de confiança de 95% (IC 95%). Hedges *g* é o tamanho do efeito da diferença entre as médias dos grupos no pós-intervenção para o desfecho escolhido, dividido pelo desvio padrão combinado para a amostra inteira e corrigida para as amostras dos pequenos estudos. Para a consistência na direção do tamanho do efeito, os valores positivos indicam níveis mais elevados para pD_2 e Rmax para o grupo exercício resistido. Já para a PAM, os valores negativos indicam um decréscimo na pressão arterial no grupo exercício resistido.

O *Forest plot* foi usado para apresentar graficamente SMD e o IC 95%. Cada estudo foi representado graficamente para gerar medidas sumarizadas, proporcional ao peso do estudo na meta-análise. Os valores inferiores a um $p < 0,05$ foram considerados estatisticamente significativos. A heterogeneidade entre os estudos foi quantificada utilizando à estatística I^2 (HIGGINS; THOMPSON, 2002). Foi adotada a categorização de heterogeneidade sugerida por Higgins e Thompson (2002), onde são considerados: baixa heterogeneidade os efeitos sumarizados que possuem percentuais de heterogeneidade inferiores a 25%; de moderada heterogeneidade os efeitos próximos a 50%; e de alta heterogeneidade quando o I^2 for superior a 75%.

Primeiramente, foi realizada uma análise de subgrupo para os resultados da PAM com base no estado de saúde do animal (ratos saudáveis vs ratos não-saudáveis), método de aferição da pressão arterial (indireta vs direto), modelo de exercício resistido (agachamento vs subida de escada), o volume de exercício (baixo vs alto), a intensidade de treinamento físico (baixa vs moderada/alta) e duração do exercício (até 8 semanas vs mais de 9 semanas). Os exercícios resistidos foram caracterizados como de baixo volume (<10 séries) e alto volume (≥ 10 séries) e a intensidade foi dividido em baixa intensidade de exercício (<60% de 1RM) e moderada/alta intensidade de exercício (≥ 60% de 1RM). A estratificação de acordo com a duração do exercício foi baseada no valor da mediana. Para as medições de pD_2 e Rmax uma análise de subgrupo foi realizada de acordo com o tipo de agonista vasodilatador.

Para avaliar o potencial de viés de publicação, um *funnel plot* foi criado por tramar o SMD individual contra seu erro padrão. Na ausência de viés, estudos maiores e mais precisos estão representados na parte superior do gráfico de forma agrupada, enquanto os estudos menores e menos precisos, mostrarão uma distribuição mais ampla abaixo do gráfico. Na presença do viés de publicação, estudos menores, relatam efeitos maiores a fim de ultrapassar os limiares de significância. Neste caso, o *funnel plot* sugere a ausência de publicação que reportam resultados negativos. Além da inspeção visual do gráfico *funnel plot*, foi realizado o teste de regressão linear de Egger's para medir a assimetria no funil. O *forest plot* e o *funnel plot* foram criados usando o *software Review Manager analysis* (RevMan, version 5.2.1: The Cochrane Collaboration, http://ims.cochrane.org/revman).

5. RESULTADO

5.1. EFFECTS OF RESISTANCE EXERCISE ON THE VASCULAR FUNCTION AND BLOOD PRESSURE IN RATS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

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EFFECTS OF RESISTANCE EXERCISE ON THE VASCULAR FUNCTION AND BLOOD PRESSURE IN RATS: A SYSTEMATIC REVIEW AND META-ANALYSIS.

Short title: Resistance exercise in rats: A meta-analysis

Silva, T.L.B.T., MSc[1], Mota, M.M., PhD[1], Fontes, M.T., MSc[1], Martins-Filho, P.R.S., PhD[2], Carvalho, V. O., PhD[3], Bonjardim, L. R., PhD[4], Santos, M.R.V., PhD[1,*].

[1] Department of Physiology, Federal University of Sergipe, 49100-000, São Cristóvão, SE, Brazil. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

[2] Department of Health Education, Federal University of Sergipe, 49060-100, Aracaju, SE, Brazil. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

[3] Department of Physiotherapy, Federal University of Sergipe, 49060000, Aracaju, SE, Brasil. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

[4] Department of Biological Sciences, Faculty of Dentistry of Bauru, University of São Paulo, 17012901, São Paulo, SP, Brazil. "This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation".

*Corresponding author: Paulo Ricardo Saquete Martins-Filho. Universidade Federal de Sergipe, Hospital Universitário, Laboratório de Patologia Investigativa. Rua Cláudio Batista, s/n. Bairro Sanatório. Aracaju, Sergipe, Brasil. CEP: 49060-100. Email address: martins-filho@ufs.br

Potential conflict of interests

We declare that there are no conflicts of interests concerning the present study.

Keywords

Meta-analysis; resistance exercise; arterial pressure; vascular; hypertension; diabetes.

Abstract

Background: Meta-analyses with preclinical studies are relatively new and promote guidelines for clinical studies. The literature has showed that the effects of resistance exercise on the cardiovascular system in experimental models are still controversy. The aim of this meta-analysis was to evaluate the effects of resistance exercise on vascular function and blood pressure in rats.

Methods: Different databases were searched for studies evaluating the effects of resistance exercise on vascular sensitivity, maximal response and blood pressure in rats up to September 30, 2014. Post-intervention between-group effect sizes were pooled with the generic inverse variance method using random-effect model and expressed as standardized mean difference, Hedges g, with 95% confidence intervals (95% CI).

Results: Thirteen eligible studies were included. Our meta-analysis showed that exercise resistance in rats does not alter the vascular sensitivity, but promotes increased vascular relaxation ($p<0.01$). In addition, we observed a reduction in blood pressure in the exercised animals ($p<0.01$). Subgroup analysis showed that squat exercise ($p<0.01$), with low volumes of resistance exercise ($p<0.05$) and with moderate/high intensity ($p<0.001$) reduces the blood pressure.

Conclusions: The results of this meta-analysis suggests that resistance exercise improves the vascular function and decreases the blood pressure in rats. However, further studies are needed to better understand the effects of different resistance exercise protocols on the cardiovascular system.

Keywords: meta-analysis; resistance exercise; arterial pressure.

1. Introduction

Resistance exercise has been indicated as a coadjuvant in the blood pressure control in humans. However, although a recent meta-analysis has showed a reduction of systolic/diastolic clinical pressures in the general population after resistance exercise [1], there is no strong evidence of the efficacy of resistance exercise on blood pressure reduction in hypertensive subjects. In addition, the effects of resistance exercise on vascular function are still not fully understand.

Some preclinical studies have showed that resistance exercise can improve the vascular function and decrease the blood pressure in healthy and diseased rats [2-7]. On the other hand, there are also experimental studies indicating the lack of efficacy of resistance exercise in reducing blood pressure in healthy rats [8,9]. These conflicting results may be related to the variables that make up the exercise protocol, including the number of sets and repetitions, workload, number of sessions per week, exercise duration, interval between sets and type of resistance exercise. In addition, other features in the experiments may explain the different effects of the resistance exercise on the cardiovascular system, such as the type of artery investigated and the animal health status.

The achievement of meta-analyses in the basic sciences is relatively new, but very promising to point out future research directions. Moreover, the translational perspective of the meta-analysis favors the guidelines for clinical studies and directs a more detailed analysis of the physiological adjustments induced by resistance exercise in animal models. Currently, a practical guide to perform meta-analyses with preclinical studies was published [10]. This meta-analysis was performed to evaluate the effects of resistance exercise on the vascular function and blood pressure in rats.

2. Methods

2.1. Search strategy

We searched on PubMed/Medline, Bireme, Embase, Lilacs, and Cochrane Library databases for original studies that evaluated the effects of resistance exercise on vascular function and blood pressure in rats. The search was performed in September 2014 and the following key words were used: "resistance exercise" and "rats". The search also included a hand search of cross-references from original articles and reviews to identify additional studies that could not be located in the electronic databases.

2.2. Eligibility criteria

Two reviewers independently screened the search results and identified potentially relevant studies based on titles and abstracts. Relevant studies were selected according to the eligibility criteria and the full texts were accessed. Disagreements between the two reviewers were resolved by consensus or by a third reviewer.

Only English full-text papers were considered for inclusion in this systematic review. Studies must have characterized the resistance exercise by repetitions, sets and resting intervals. Studies involving healthy rats or those with chronic diseases were also included in this systematic review. Studies involving any other animal species or any other type of exercise such as aerobic exercises were excluded.

2.3. Outcomes

Our main outcomes of interest were the arterial relaxation induced by vasoactive agents and mean blood pressure (MBP). The arterial relaxation was represented by vascular sensitivity (pD_2), which corresponds to the negative logarithm of the molar concentration of agonist that determines a response equal to 50% of the maximal response (EC_{50}), and the maximal response (Rmax) which corresponds to the maximal relaxant effect of the vasoactive agent. If the article does not present the MBP values, these were calculated from the systolic and diastolic pressures (MBP= SBP + (DBPx2)/3). Any other required information was requested via e-mail to the corresponding author of the original article.

2.4. Data extraction

Data extraction was independently performed by two reviewers using a predefined protocol. Disagreements between the two reviewers were also resolved by consensus or by a third reviewer. The data were recorded considering the animal species, sample size, study group analysis, sample characteristics, characterization of the exercise protocol, duration of the intervention, instruments, type of artery, outcomes of vascular relaxation and MBP.

2.5. Quality assessment of included studies

The methodological quality of the included studies was assessed by two independent reviewers following the criteria adapted by Van Drongelen et al. [11] and Schmidt et al. [12]: 1) randomization; 2) compliance with animal welfare regulations; 3) aged and/or weight; 4) number of animals used per study; 5) drugs and reagents described in the methodology (manufacturer); 6) physiological responses of ≥ 5 measurements per experiment; 7) monitoring of physiological parameters (temperature, blood pressure, vascular reactivity, blood biochemical profile, morphology, cardiac function); 8) training protocol described in the methodology; 9) animal familiarization with the training protocol; 10) one repetition maximum test (1RM) or maximal load assessment. The studies were thus classified into 2 categories of quality (category I, 6-10 items; high quality and category II, 0-5 items; low quality).

2.6. Statistical analysis

Post-intervention between-group effect sizes were pooled with the generic inverse variance method using random-effect model and expressed as standardized mean difference (SMD), Hedges *g*, with 95% confidence intervals (95% CI). Hedges *g* effect size is the between-group difference on the post-intervention mean scores for the chosen outcome measure, divided by the pooled standard deviation for entire sample, and then corrected for small study samples. For consistency in the direction of effect sizes, positive values denote higher levels of pD_2 and Rmax with the resistance exercise. For the MBP, negative values indicate a decrease in the blood pressure in the resistance group.

Forest plot was used to graphically present the pooled SMD and the 95% CI. Each study was represented by a square in the plot, proportional to the study's weight in the meta-analysis. Two-sided p-values lower than 0.05 were considered statistically significant. Between-study heterogeneity was quantified using the I^2-statistic [13] and a high degree of inconsistency was considered if values were higher than 75%.

A priori subgroup analyses for the outcome of MBP were conducted based on health status (healthy rats *vs* diseased rats), pressure measurement (indirect *vs* direct), type of exercise (squat *vs* ladder adapted), volume of exercise (low *vs* high), exercise training intensity (low *vs* moderate/high), and exercise duration (< 8 weeks *vs* ≥ 8 weeks). Resistance exercise was characterized as low volume (< 10 series) and high volume (≥ 10 series) and the intensity was divided into low intensity (< 60% of 1RM) and moderate/ high intensity (≥ 60% of 1RM). Stratification according to exercise duration was based on the median value.

To examine the potential for publication bias, a funnel plot was created by plotting the individual SMD against its standard error. In the absence of bias, larger and more precise studies are plotted at the top, near the combined effect size, while smaller and less precise studies will show a wider distribution below. In the presence of publication bias, smaller studies report larger effects in order to exceed arbitrary significance thresholds. In this case, it suggests that studies that might have reported negative results may not have been published [14]. In addition to the visual inspection of the funnel plot, Egger's linear regression test was performed to measure the funnel plot asymmetry [15]. The forest and funnel plots were created using the Review Manager Analysis software (RevMan, version 5.2.1: The Cochrane Collaboration, http://ims.cochrane.org/revman).

3. Results

3.1. Characteristics of included studies

Our search strategy found 1.072 articles about resistance exercise in rats (Figure 1). After the initial screening, 1.055 articles were excluded and only 18 full-text articles were eligible. These studies evaluated the effect of resistance exercise on the vascular function and blood pressure. Then, 5 articles were excluded because the authors did not describe the numerical data of averages [5,16,17] or did not evaluate the outcomes of interest for this systematic review [18,19]. For articles that did not describe the numerical data in the results section, the authors were contacted via e-mail. In case of no response in 14 days, the study was excluded from our review [5,16,17]. Thus, this review included 13 studies for quantitative analysis related to vascular function (pD_2 and Rmax) and blood pressure [2-4,6-9,20-25] (Figure 1). The characteristics of the studies included in this systematic review are shown in Table 1.

All studies were performed in healthy/diseased rats (Wistar, Sprague-Dawley, SHR and Fisher) which were submitted to the resistance exercise ranging from a session up to 14 weeks of training. The studies included showed high methodological quality, according to criteria adopted for this review (Class I, 6-10 items; Table 2).

3.2. Effects of the resistance exercise on vascular response

The meta-analysis of the effects of resistance exercise on arterial sensitivity showed no changes in pD_2 (Figure 2). On the other hand, the overall effect size of the resistance exercise showed an increased in the Rmax (p=0.003) (Figure 3).

3.3. Effects of the resistance exercise on blood pressure

Our meta-analysis demonstrated that resistance exercise was effective in reducing MBP in exercised animals (p< 0.01). Subgroup analysis showed a decrease in MPB in diseased rats (p<0.01). In addition, both methods of measurements (indirect and direct) were effective in demonstrating changes in blood pressure in the exercised animals (p< 0.01; p< 0.05, respectively; Table 3).

Regarding to the model and protocol of resistance exercise, this meta-analysis showed that the squat exercise (p< 0.01), low-volume (p< 0.05) and moderate- / high-intensity- exercises (p< 0.001) were effective in reducing the MBP (Table 3). Considering the exercise training period, the meta-analysis indicates that the squat exercises were effective in reducing the MBP in the first 8 weeks of training (p< 0.001, Table 4).

3.4. Publication bias

We explored potential for publication bias for the reduction of MBP after the resistance exercise using a funnel plot and Egger's test. Visual inspection of the funnel plot reveals overt asymmetry due to the presence of small-study effects (Figure 5). Egger's regression test showed evidence for publication bias (p = 0.001).

4. Discussion

This systematic review and meta-analysis was composed by 13 high-quality methodological studies that demonstrated the efficacy of resistance exercise training in the improvement of arterial vasodilation and reduction of blood pressure in rats. Basic science has made efforts in the development of devices that mimic the performance of resistance exercise in animals [26]. The most common resistance exercise models to assess cardiovascular function in rats are the squat exercise and stair-climbing protocol [27,28]. Recently, some studies have demonstrated the efficacy of resistance exercise in promoting beneficial cardiovascular adjustments in healthy, diabetic and hypertensive rats [2-7]. Nevertheless, the effects of resistance exercise on cardiovascular parameters in humans and animals are not fully understood.

It is described that exercise-induced vascular stress releases vasoactive substances that regulate vascular tone [29]. The vascular function, represented by pD_2 and Rmax, can be assessed in isolated vessels via concentration-response curves induced by agonists, such as acetylcholine, insulin and sodium nitroprusside [2-4,7]. We observed in this meta-analysis that resistance exercise does not affect pD_2 in the vascular relaxation induced by acetylcholine and nitroprusside. However, Faria et al. [7] demonstrated greater acetylcholine-induced vascular sensitivity in hypertensive rats that performed a resistance exercise session with 20 sets of 15 repetitions and 50% of the maximal voluntary contraction. Similarly, a study performed by Araujo et al. [4] showed that four weeks of resistance exercise with 3 sets of 10 repetitions with 50% of the maximal voluntary contraction increased arterial sensitivity induced by nitroprusside in hypertensive animals. This evidence is not conclusive and further studies are needed to evaluate the effect on endothelium-dependent and endothelium-independent vascular sensitivity in different animal models.

In a previous systematic review, Jasperse and Laughlin [30] concluded that aerobic exercise does not increase vascular function in healthy rats, but can reverse the endothelial dysfunction that accompanies various diseases. The present study shows that resistance exercise can increase vascular function induced by insulin and acetylcholine in healthy animals and those with hypertension and/or diabetes. An interesting fact is that some studies included in our meta-analysis observed vasodilation in the mesenteric artery and tail artery, which are not directly involved with the blood flow of the exercised muscles. These results indicate that resistance exercise seems to promote a generalized vascular effect, which directly contributes to the control of the blood pressure [2,3,7].

The results of our meta-analysis reinforce the fact that resistance exercise in general reduces MBP in rats and may be an important tool to understand blood pressure control mechanisms. The subgroup analysis indicated that the effects of lowering blood pressure through the resistance exercise are more evident in diseased animals and using either direct or indirect methods. In addition, we showed that the squat exercise model for rats developed by Tamaki [27] was more efficient in increasing vascular function and lowering blood pressure in rats. In this exercise model, the animal performs the movement by electrical stimulation. Studies have showed that the electrical stimulation parameters adopted by Tamaki do not interfere in vascular, hemodynamic, morphological and hormonal parameters involving the cardiovascular system [2,5,6]. Recently, a new resistance exercise model for rats composed by sound devices, light and feeding to induce the animal to perform the movement was developed [31]. Taking into account the limitations in extrapolating the basic science results, we must improve the translation of the results for the clinical studies using models and resistance exercise programs that are similar to that performed in humans.

Subgroup analysis showed that resistance exercises with low volume, high intensity and duration of up to 8 weeks reduced the MBP in rats. In humans, recent scientific evidence indicates that high-intensity resistance exercise appears to be effective in lowering blood pressure in healthy young and hypertensive elderly [32,33]. In contrast, another study showed that low-resistance exercise intensities led to changes in blood pressure without clinical relevance in men with and without hypertension [34]. Currently, it seems that moderate/high intensities can contribute for the blood pressure reduction in both humans and animals [5-7,32,33]. Unfortunately, we were unable to perform a meta-regression analysis in order to explain the high between-study heterogeneity and better understood the influence of different protocols of resistance exercise on the blood pressure.

For some years, resistance exercise in humans was contraindicated in the treatment of cardiovascular disorders. Nowadays, considering that aerobic training is well established in the literature in the reduction of blood pressure in hypertensive individuals, some authors suggested that the resistance exercise should be performed in association with aerobic exercise [35-37]. In this way, the results of the present study may contributed to the knowledge of effects of resistance exercise on the cardiovascular system.

4.1. Study limitations

Although this is the first systematic review and meta-analysis to investigate the effects of the resistance exercise on the cardiovascular parameters in rats, there are some limitations. First, despite the efforts that were made to capture all available published studies, a potential for publication bias was observed for the MBP outcome. However, a recent meta-analysis indicated that publication bias may be quite common in preclinical studies [38]. Second, a small number of studies that assessed the pD_2 and Rmax on the vascular response were included, and it was not possible to perform a subgroup analysis according to the volume, intensity, frequency, duration, type of resistance exercise, type of artery and animal health. In addition, the influence of the weekly frequency of resistance exercise on MBP was not evaluated. Finally, we were unable to perform a meta-regression to explore potential sources of heterogeneity and better understood the influence of different protocols of resistance exercise on the blood pressure. Despite these limitations, this systematic review and meta-analysis can be used as a possible tool for design of new preclinical studies to evaluate the cardiovascular adjustments provided the resistance exercise.

5. Conclusion

The results of this meta-analysis suggest that resistance exercise improves the vascular function and reduces blood pressure in rats. Although subgroup analyses for MBP have indicated that resistance exercise is more effective in reducing blood pressure in diseased rats, using a squat apparatus, with low volume, moderate to high intensity, and in 8 weeks of training, more evidence is needed for a better understanding of the effects of resistance exercise on the cardiovascular system.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest

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Figure captions

Figure 1. Flow chart of the search strategy and selection of articles

Figure 2. Effects of the resistance exercise on the vascular sensitivity. The effects of the resistance exercise made in pD_2 are described as SMD and its 95% CI. The subgroup analyses indicate the effectiveness of the resistance exercise in the activation of relaxation by agonists. * Even study with different agonists; # Healthy group (sedentary vs exercised); ## Diseased group (sedentary vs exercised).

Figure 3. Effects of the resistance exercise on the maximal vascular response. The effects of the resistance exercise made in Rmax are described as SMD and its 95% CI. The subgroup analyses indicate the effectiveness of the resistance exercise in the activation of relaxation by agonists. * Even study with different agonists; # Healthy group (sedentary vs exercised); ## Diseased group (sedentary vs exercised).

Figure 4. Effects of the resistance exercise on blood pressure. The effects of the resistance exercise made in MBP are described as SMD and its 95% CI. # Healthy group (sedentary vs exercised); ## Diseased group (sedentary vs exercised).

Figure 5. Funnel plot of publication bias for the reduction of mean blood pressure.

Table captions

Table 1. Characteristics of included studies.

Table 2. Quality assessment of included studies.

Table 3. Subgroup analysis for mean blood pressure.

Table 4. Subgroup analysis according to exercise duration for mean blood pressure.

Figure1
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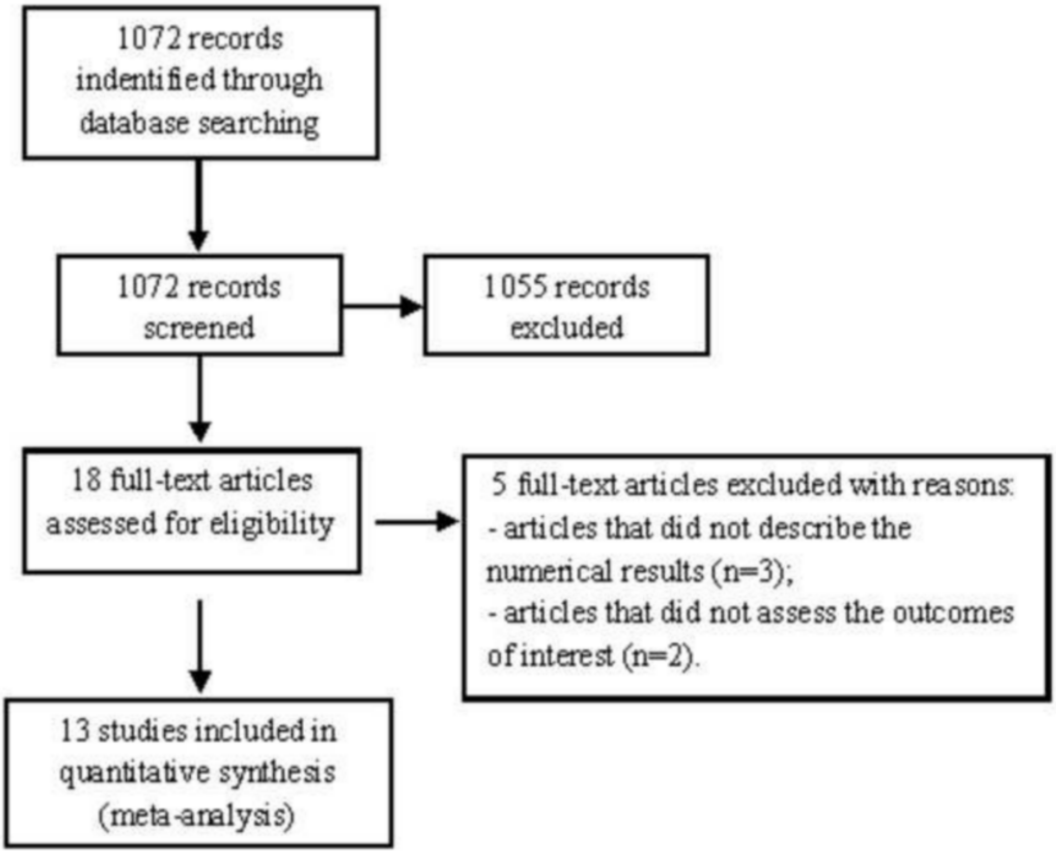

Figure2
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Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Acetylcholine				
Faria et al.##	5.1742	1.1662	11.9%	5.17 [2.89, 7.46]
Figard et al.##	2.3232	0.6883	14.6%	2.32 [0.97, 3.67]
Mota et al.##	-2.1141	0.6598	14.8%	-2.11 [-3.41, -0.82]
Subtotal (95% CI)			**41.2%**	**1.71 [-2.26, 5.69]**
Heterogeneity: Tau² = 11.59; Chi² = 38.46, df = 2 (P < 0.00001); I² = 95%				
Test for overall effect: Z = 0.84 (P = 0.40)				
1.1.2 Sodium nitroprusside				
Araújo et al.##	3.8894	1.1277	12.1%	3.89 [1.68, 6.10]
Faria et al.*##	-0.9452	0.5358	15.4%	-0.95 [-2.00, 0.10]
Harris et al.#	0.2363	0.4492	15.7%	0.24 [-0.64, 1.12]
Harris et al.##	-0.4063	0.4776	15.6%	-0.41 [-1.34, 0.53]
Subtotal (95% CI)			**58.8%**	**0.36 [-0.95, 1.66]**
Heterogeneity: Tau² = 1.37; Chi² = 15.96, df = 3 (P = 0.001); I² = 81%				
Test for overall effect: Z = 0.53 (P = 0.59)				
Total (95% CI)			**100.0%**	**0.94 [-0.53, 2.40]**
Heterogeneity: Tau² = 3.35; Chi² = 56.87, df = 6 (P < 0.00001); I² = 89%				
Test for overall effect: Z = 1.26 (P = 0.21)				
Test for subgroup differences: Chi² = 0.40, df = 1 (P = 0.53), I² = 0%				

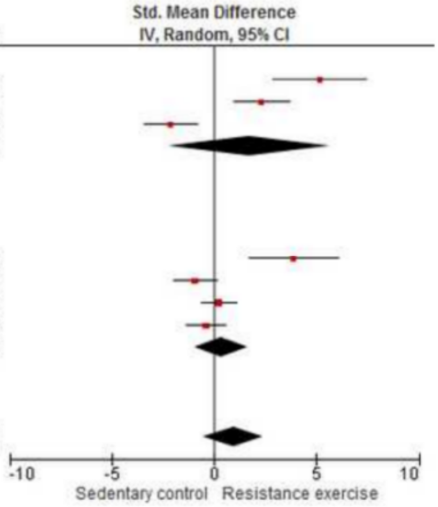

Fig 2

Figure3
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Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Insulin				
Fontes et al.#	5.6858	1.0984	10.4%	5.69 [3.53, 7.84]
Subtotal (95% CI)			**10.4%**	**5.69 [3.53, 7.84]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.18 (P < 0.00001)				
1.2.2 Acetylcholine				
Faria et al.##	0.5244	0.5113	13.7%	0.52 [-0.48, 1.53]
Figard et al.##	4.4063	1.0271	10.8%	4.41 [2.39, 6.42]
Harris et al.#	-0.2714	0.4498	14.0%	-0.27 [-1.15, 0.61]
Harris et al.##	0.4976	0.4807	13.9%	0.50 [-0.44, 1.44]
Mota et al.##	3.4518	0.8625	11.8%	3.45 [1.76, 5.14]
Subtotal (95% CI)			**64.3%**	**1.50 [0.09, 2.90]**
Heterogeneity: Tau² = 2.10; Chi² = 28.11, df = 4 (P < 0.0001); I² = 86%				
Test for overall effect: Z = 2.09 (P = 0.04)				
1.2.3 Sodium nitroprusside				
Araújo et al.##	2.8123	0.9077	11.5%	2.81 [1.03, 4.59]
Faria et al.*##	0	0.5	13.8%	0.00 [-0.98, 0.98]
Subtotal (95% CI)			**25.3%**	**1.30 [-1.44, 4.05]**
Heterogeneity: Tau² = 3.42; Chi² = 7.36, df = 1 (P = 0.007); I² = 86%				
Test for overall effect: Z = 0.93 (P = 0.35)				
Total (95% CI)			**100.0%**	**1.90 [0.65, 3.16]**
Heterogeneity: Tau² = 2.71; Chi² = 55.08, df = 7 (P < 0.00001); I² = 87%				
Test for overall effect: Z = 2.98 (P = 0.003)				
Test for subgroup differences: Chi² = 11.10, df = 2 (P = 0.004), I² = 82.0%				

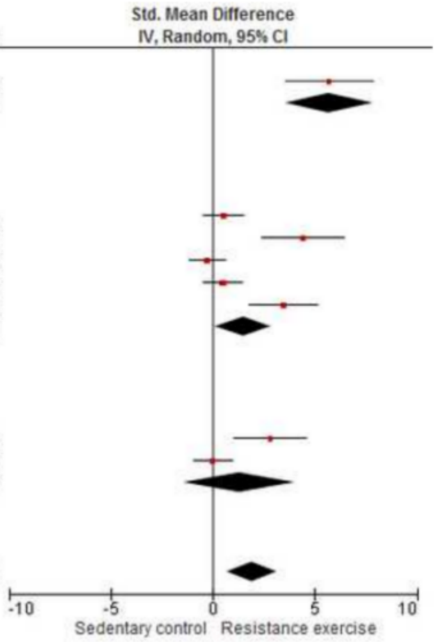

Fig 3

Figure4
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Fig 4

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
Araújo et al.##	-2.6157	0.8705	5.8%	-2.62 [-4.32, -0.91]
Barauna et al.#	-0.4767	0.5894	7.2%	-0.48 [-1.63, 0.68]
de Cássia et al.#	-1.5144	0.4842	7.7%	-1.51 [-2.46, -0.57]
Faria et al ##	-2.704	0.7437	6.4%	-2.70 [-4.16, -1.25]
Grans et al.#	-0.2215	0.502	7.7%	-0.22 [-1.21, 0.76]
Grans et al.##	0.4727	0.5092	7.6%	0.47 [-0.53, 1.47]
Leite et al ##	-2.3151	0.6872	6.7%	-2.32 [-3.66, -0.97]
Leite et al.#	-1.3529	0.5709	7.3%	-1.35 [-2.47, -0.23]
Lizardo et al.##	-2.5386	0.5859	7.2%	-2.54 [-3.69, -1.39]
Mostarda et al.#	0.2438	0.5025	7.7%	0.24 [-0.74, 1.23]
Mostarda et al.##	0.5292	0.5115	7.6%	0.53 [-0.47, 1.53]
Mota et al.##	-3.257	0.8305	6.0%	-3.26 [-4.88, -1.63]
Silveira et al.#	0.8456	0.5288	7.5%	0.85 [-0.19, 1.88]
Silveira et al.##	-0.8456	0.5288	7.5%	-0.85 [-1.88, 0.19]
Total (95% CI)			**100.0%**	**-1.03 [-1.71, -0.35]**

Heterogeneity: Tau² = 1.33; Chi² = 65.06, df = 13 (P < 0.00001); I² = 80%
Test for overall effect: Z = 2.97 (P = 0.003)

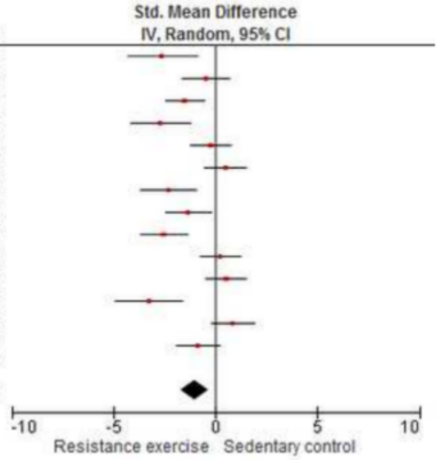

Figure5
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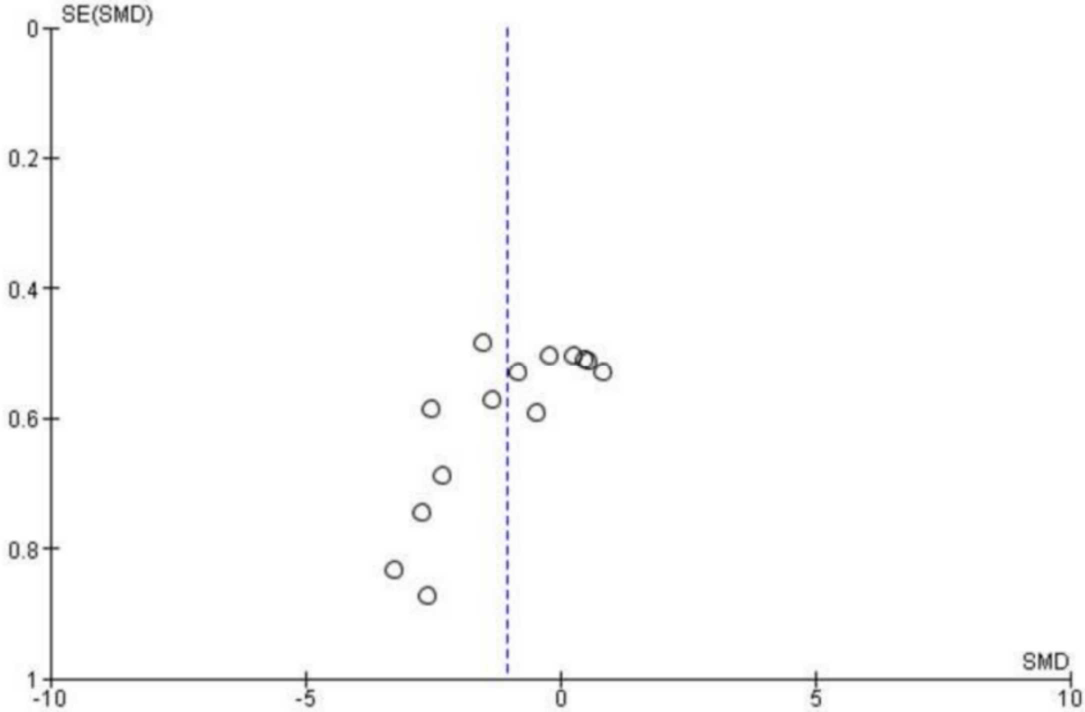

Fig 5

Table1

Table 1.

First Author/ Year of Publication	Rat (Species/ Mode)	Resistance exercise (Mode)	Physiological variable measurements	Duration/ Frequency (days/ week)	Volume / Intensity/ Resting period
Araujo et al., 2013	Wistar (M, hypertensive)	Squat	Vascular function, blood pressure	4 weeks/ 3 days	3x10/ 50%/ 60 s
Barauna et al., 2008	Wistar (M, health)	Squat	Blood pressure	8 weeks/ 5 days	4x12/ 65-75%/ 90 s
de Cássia et al., 2008	Wistar (M, health)	Squat	Blood pressure	8 weeks/ 5 days	5x12/ 60 and 75%/ 90 s
Faria et al., 2010	SHR (M, hypertensive)	Squat	Vascular function, blood pressure	Single session	20x15/ 50%/ 60 s
Figard et al., 2006	Sprague–Dawley (F, ovariectomy)	Isometric strength	Vascular function	14 weeks/ 5 days	Duration and intensity were gradually increased
Fontes et al., 2014	Wistar (M, health)	Squat	Vascular function	Single session	15x10/ 70%/ 180 s
Grans et al., 2014	Wistar (M, health)	Ladder adapted	Blood pressure	12 weeks/ 5 days	15 climbings per session/ 40-60%/ 60 s
Harris et al., 2010	Fisher (M, health)	Ladder	Vascular function	6 weeks/ 3 days	6-8 climbings per

		adapted			session/ 50%/ 120 s
Leite et al., 2013	Wistar (M, health and obese)	Ladder adapted	Blood pressure	12 weeks/ 3 days	4 climbings per session/ 50%, 75%, 90% and 100%/ 120 s
Lizardo et al., 2008	SHR (M, hypertensive)	Squat	Blood pressure	Single session	20x10/ 70%/ 120 s
Mostarda et al., 2014	Wistar (M, health and diabetic)	Squat	Blood pressure	10 weeks/ did not find	4x20/ 40%/ 90 s, and sixth to tenth week, 4x30/ 40%/ 90 s
Mota et al., 2014	Wistar (M, diabetic)	Squat	Vascular function, blood pressure	8 weeks/ 3 days	3x10/ 50%/ 60 s
Silveira et al., 2011	Wistar (F, ovariectomy)	Ladder adapted	Blood pressure	10 weeks/ 3 days	6-7 climbings per session/ ?/ 120 s

M, male; F, female; s, second.

Table2

Table 2.

Study	1	2	3	4	5	6	7	8	9	10	Score/ %
Araujo et al., 2013	-	+	+	+	+	-	+	+	+	+	8/ 80%
Barauna et al., 2008	-	+	-	+	+	+	+	+	+	+	8/ 80%
de Cássia et al., 2008	+	+	+	+	+	+	+	+	+	+	10/100%
Faria et al., 2010	+	+	+	-	+	+	+	+	+	+	9/ 90%
Figard et al., 2006	+	+	+	+	+	+	+	+	-	-	8/ 80%
Fontes et al., 2014	+	+	+	+	-	+	-	+	+	+	8/ 80%
Grans et al., 2014	+	+	+	+	-	+	+	+	+	+	9/ 90%
Harris et al., 2010	-	+	+	+	-	+	+	+	-	+	7/ 70%
Leite et al., 2013	+	+	+	+	+	+	+	+	+	+	10/ 100%
Lizardo et al., 2008	+	+	+	+	-	+	-	+	-	+	7/ 70%
Mostarda et al., 2014	+	+	+	+	+	+	+	+	-	+	9/ 90%
Mota et al., 2014	-	+	+	+	+	+	+	+	+	+	9/ 90%
Silveira et al., 2011	-	+	+	+	-	+	+	+	+	-	7/ 70%

(category I, 6-10 items; high quality and category II, 0-5 items; low quality)

Table3

Table 3.

Subgroups	Exercise groups	I^2 (%)	SMD (95% CI)
Health status			
Healthy rats	6	68	-0.41 (-1.15,0.33)
Diseased rats	8	84	-1.58 (-2.67,-0.49)**
Pressure measurement			
Indirect (tail cuff)	3	0	-1.92 (-2.69,-1.15)***
Direct (intra-arterial)	11	81	-0.78 (-1.54,-0.02)*
Type of exercise			
Squat	8	82	-1.45 (-2.46,-0.44)**
Ladder adapted	6	75	-0.52 (-1.39,0.36)
Volume			
Low	10	79	-0.97 (-1.76,-0.19)*
High	4	87	-1.19 (-2.75,0.36)
Intensity			
Low	7	83	-0.94 (-2.04,0.15)
Moderate/high	5	47	-1.61 (-2.31,-0.92)***

I^2-statistic: Heterogeneity; SMD: Standardized Mean Difference.
*p<0.05; **p<0.01; ***p<0.001*p<0.05; **p<0.01; ***p<0.001

Table4

Table 4.

Type of exercise	Exercise duration	Exercise groups	I^2 (%)	SMD (95% CI)
Squat	< 8 weeks	4	66	-2.02 (-3.18,-0.87)***
	≥ 8 weeks	4	86	-0.90 (-2.37,0.56)
Ladder adapted	< 8 weeks	0	Not applicable	Not estimable
	≥ 8 weeks	6	75	-0.52 (-1.39,0.36)

I^2-statistic: Heterogeneity; SMD: Standardized Mean Difference.
*p<0.05; **p<0.01; ***p<0.001

6. CONCLUSÃO

O exercício resistido aumenta a Rmax (vascular) em ratos. Nas análises de subgrupo para a PAM os resultados indicam que o exercício resistido é mais eficaz em reduzir a pressão arterial de:

- Ratos doentes que executaram o exercício de agachamento com baixo volume, intensidade de moderada/alta e uma duração de até 8 semanas de treinamento.

7. PERSPECTIVAS

As perspectivas para os resultados da presente tese é que possam auxiliar na translação do conhecimento pré-clínico para o desenvolvimento de novos estudos clínicos. Os estudos pré-clínicos com o exercício físico é uma prática relativamente nova e são importantes para identificar os mecanismos que envolvem a prevenção e o tratamento das doenças cardiovasculares. Futuros estudos pré-clínicos com métodos mais homogênios são necessários para a compreensão dos efeitos do exercício resistido no sistema cardiovascular. Dentro desta perspectiva, as revisões sistemáticas com meta-análise podem ser uma importante ferramenta metodológica para direcionar os estudos experimentais e clínicos que envolvem o exercício físico.

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9. ANEXOS

9.1. ANEXO A- Instruções aos Autores (International Journal of Cardiology**)**

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AUTHOR INFORMATION PACK

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[2] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.
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9.2. ANEXO B- Comprovante de Submissão.

Elsevier Editorial System(tm) for International Journal of Cardiology
Manuscript Draft

Manuscript Number:

Title: EFFECTS OF RESISTANCE EXERCISE ON THE VASCULAR FUNCTION AND BLOOD PRESSURE IN RATS: A SYSTEMATIC REVIEW AND META-ANALYSIS

Article Type: Original Article

Keywords: meta-analysis; resistance exercise; arterial pressure

Corresponding Author: Prof. Paulo Ricardo S Martins-Filho, PhD

Corresponding Author's Institution: Federal University of Sergipe

First Author: Tharciano Luiz B Silva, Msc

Order of Authors: Tharciano Luiz B Silva, Msc; Marcelo M Mota, PhD; Milene T Fontes, Msc; Paulo Ricardo S Martins-Filho, PhD; Vitor O Carvalho, PhD; Leonardo R Bonjardim, PhD; Márcio Roberto V Santos, PhD

Manuscript Region of Origin: BRAZIL

Abstract: Background: Meta-analyses with preclinical studies are relatively new and promote guidelines for clinical studies. The literature has showed that the effects of resistance exercise on the cardiovascular system in experimental models are still controversy. The aim of this meta-analysis was to evaluate the effects of resistance exercise on vascular function and blood pressure in rats.
Methods: Different databases were searched for studies evaluating the effects of resistance exercise on vascular sensitivity, maximal response and blood pressure in rats up to September 30, 2014. Post-intervention between-group effect sizes were pooled with the generic inverse variance method using random-effect model and expressed as standardized mean difference, Hedges g, with 95% confidence intervals (95% CI).
Results: Thirteen eligible studies were included. Our meta-analysis showed that exercise resistance in rats does not alter the vascular sensitivity, but promotes increased vascular relaxation ($p<0.01$). In addition, we observed a reduction in blood pressure in the exercised animals ($p<0.01$). Subgroup analysis showed that squat exercise ($p<0.01$), with low volumes of resistance exercise ($p<0.05$) and with moderate/high intensity ($p<0.001$) reduces the blood pressure.
Conclusions: The results of this meta-analysis suggests that resistance exercise improves the vascular function and decreases the blood pressure in rats. However, further studies are needed to better understand the effects of different resistance exercise protocols on the cardiovascular system.

Suggested Reviewers: Thais de O Faria PhD
Department of Physiological Sciences, Federal University of Espirito Santo
thais_oliveirafaria@hotmail.com

Richard D Leite PhD
Departament of Physical Education, Federal University of Maranhão
rdleite@gmail.com

10. APÊNDICES

10.1. APÊNDICE A- FORMULÁRIO DE EXTRAÇÃO DOS DADOS

1. Pesquisador:

( ) Pesquisador 1

( ) Pesquisador 2

2. Informações gerais:

2.1. Título do estudo:
____
____

2.2. Autores:
____
____

2.3. Nome completo do Jornal/Revista, volume, página e ano de publicação:
____

2.4. Palavras-chave:
____

3. Informações específicas:

3.1. Objetivo do estudo:
____
____

3.2. Critérios de inclusão e exclusão:
____
____

3.3. Tamanho total da amostra:___________

3.4. Tamanho amostral por grupo incluso no estudo:

3.4.1. Grupo sedentário (saudável):_______
3.4.2. Grupo exercitado (saudável):_______
3.4.3. Grupo sedentário (doente):________
3.4.4. Grupo exercitado (doente):________

3.4. Características gerais da amostra:

____

____

3.5. Análises estatísticas:

____

____

____

____

4. Protocolo de exercício físico resistido para ratos:

4.1. Modelo de exercício físico resistido para ratos:____________________
4.2. Característica da sessão de exercício:__________________________
4.3. Frequência do exercício:_________________________________
4.4. Duração da sessão de exercício:____________________________
4.5. Volume, intensidade e intervalo de repouso:____________________

5. Técnicas de mensuração:

5.1. Função vascular:_____________________________________
5.2. Pressão arterial:_____________________________________

6. Desfechos do artigo avaliado:

6.1. Primário:____
6.2. Secundário:______________________________________

6. Desfechos de interesse para a pesquisa:

( ) Função Vascular ( ) Pressão arterial

7. Extração dos dados:

FUNÇÃO VASCULAR											
Animais saudáveis (pD_2)						**Animais doentes (pD_2)**					
Grupo sedentário			**Grupo exercitado**			**Grupo sedentário**			**Grupo exercitado**		
n:			**n:**			**n:**			**n:**		
Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M
Animais saudáveis (Rmax)						**Animais doentes (Rmax)**					
Grupo sedentário			**Grupo exercitado**			**Grupo sedentário**			**Grupo exercitado**		
n:			**n:**			**n:**			**n:**		
Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M
Agonista:											

pD_2: representa a sensibilidade vascular ao agonista. Rmax: representa a resposta vascular máxima ao agonista. n: número amostral. DP: desvio padrão. E.P.M: erro padrão da média.

PRESSÃO ARTERIAL											
Animais saudáveis (PAS)						**Animais doentes (PAS)**					
Grupo sedentário			**Grupo exercitado**			**Grupo sedentário**			**Grupo exercitado**		
n:			**n:**			**n:**			**n:**		
Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M
Animais saudáveis (PAD)						**Animais doentes (PAD)**					
Grupo sedentário			**Grupo exercitado**			**Grupo sedentário**			**Grupo exercitado**		
Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M
Animais saudáveis (PAM)						**Animais doentes (PAM)**					
Grupo sedentário			**Grupo exercitado**			**Grupo sedentário**			**Grupo exercitado**		
Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M	Média	DP	E.P.M

PAS: pressão arterial sistólica. PAD: pressão arterial diastólica. PAM: pressão arterial média. n: número amostral. DP: desvio padrão. E.P.M: erro padrão da média.

7. Extração dos dados para a análise da qualidade do estudo:

Itens coletados e categorização

7.1. Randomização:
( ) Negativo ( ) Positivo
7.2. Cumprimento dos regulamentos de bem-estar animal;
( ) Negativo ( ) Positivo
7.3. Idade e/ou peso do animal:
( ) Negativo ( ) Positivo
7.4. Número claro de animais utilizados para o estudo:
( ) Negativo ( ) Positivo
7.5. Drogas e reagentes descritos na metodologia (fabricante):
( ) Negativo ( ) Positivo
7.6. Respostas fisiológicas ≥ que 5 medições por experimento:
( ) Negativo ( ) Positivo
7.7. Verificação de parâmetros fisiológicos (temperatura, pressão arterial, reatividade vascular, sangue perfil bioquímico, morfologia, função cardíaca);
( ) Negativo ( ) Positivo
7.8. Protocolo de exercício descrito na metodologia:
( ) Negativo ( ) Positivo
7.9. Familiarização do animal com o protocolo de treinamento:
( ) Negativo ( ) Positivo
7.10. Teste de uma repetição máxima (1 RM) ou carga máxima:
( ) Negativo ( ) Positivo

10.2. APÊNDICE B- Resistance exercise acutely enhances mesenteric artery insulin-induced relaxation in healthy rats. Life sciences. 94(1):24-9, 2014.

Life Sciences 94 (2014) 24–29

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Resistance exercise acutely enhances mesenteric artery insulin-induced relaxation in healthy rats

M.T. Fontes [a], T.L.B.T. Silva [a], M.M. Mota [a], A.S. Barreto [a], L.V. Rossoni [b], M.R.V. Santos [a,*]

[a] Department of Physiology, Federal University of Sergipe, 49100-000, São Cristóvão, SE, Brazil
[b] Department of Physiology and Biophysics, Institute of Biomedical Sciences, University of Sao Paulo, 05508-900, São Paulo, SP, Brazil

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ABSTRACT

Aims: We evaluated the mechanisms involved in insulin-induced vasodilatation after acute resistance exercise in healthy rats.
Main methods: Wistar rats were divided into 3 groups: control (CT), electrically stimulated (ES) and resistance exercise (RE). Immediately after acute RE (15 sets with 10 repetitions at 70% of maximal intensity), the animals were sacrificed and rings of mesenteric artery were mounted in an isometric system. After this, concentration–response curves to insulin were performed in control condition and in the presence of LY294002 (PI3K inhibitor), L-NAME (NOS inhibitor), L-NAME + TEA (K^+ channels inhibitor), LY294002 + BQ123 (ET-A antagonist) or ouabain (Na^+/K^+ ATPase inhibitor).
Key findings: Acute RE increased insulin-induced vasorelaxation as compared to control (CT: $R_{max} = 7.3 \pm 0.4\%$ and RE: $R_{max} = 15.8 \pm 0.8\%$; $p < 0.001$). NOS inhibition reduced ($p < 0.001$) this vasorelaxation from both groups (CT: $R_{max} = 2.0 \pm 0.3\%$, and RE: $R_{max} = -1.2 \pm 0.1\%$), while PI3K inhibition abolished the vasorelaxation in CT ($R_{max} = -0.1 \pm 0.3\%$, $p < 0.001$), and caused vasoconstriction in RE ($R_{max} = -6.5 \pm 0.6\%$). That insulin-induced vasoconstriction on PI3K inhibition was abolished ($p < 0.001$) by the ET-A antagonist ($R_{max} = 2.9 \pm 0.4\%$). Additionally, acute RE enhanced ($p < 0.001$) the functional activity of the ouabain-sensitive Na^+/K^+ ATPase activity ($R_{max} = 10.7 \pm 0.4\%$) and of the K^+ channels ($R_{max} = -6.1 \pm 0.5\%$; $p < 0.001$) in the insulin-induced vasorelaxation as compared to CT.
Significance: Such results suggest that acute RE promotes enhanced insulin-induced vasodilatation, which could act as a fine tuning to vascular tone.

Introduction

Several authors have demonstrated the ability of exercise to prevent cardiovascular risk factors, among them endothelial dysfunction (Di Francescomarino et al., 2009; Golbidi and Laher, in press; Green et al., 2004; Zanesco and Antunes, 2007). The literature has demonstrated the ability of both chronic and acute aerobic exercise to improve the insulin signaling pathway involved not only in the glucose metabolism but also in the vascular modulation (Caponi et al., 2013; Pauli et al., 2010; Yang et al., 2006, 2010). In particular, resistance exercise has been also used for improvement of diabetes, hypertension and obesity (Westcott, 2012). Nevertheless, the signaling pathways are not clear.

Hemodynamic effects of insulin occur for two different endothelium-dependent signaling pathways: IR/PI3K/eNOS, responsible for the relaxant effect, and IR/MAPK/ET-1, responsible for the contractile effect (Chaudhuri et al., 2012; Montagnani et al., 2001; Muniyappa and Quon, 2007; Salt, 2013). Thus, the balance between the release of NO and ET-1 plays an important role for the control of vascular tone and blood flow adjustments in response to the exercise (Mather et al., 2001; Muniyappa and Sowers., 2013).

Previous studies have shown that insulin-induced vasorelaxation is enhanced in animals after aerobic exercise. This enhancement is caused by the increase of NO release, associated to K^+ channels-induced hyperpolarization (Ghafouri et al., 2011; Rossi et al., 2005; Yang et al., 2006, 2010). Additionally, Aughey et al. (2007) showed that aerobic exercise can change the activity and expression of skeletal muscle Na^+/K^+-ATPase in humans. In vascular smooth muscle, Garland et al. (2011), Marín and Redondo (1999), and Smith et al. (1997) demonstrated that Na^+/K^+-ATPase activity may be influenced by the endothelium and K^+ channels. However, there are no data in the literature showing the effect of resistance exercise on the insulin-induced relaxation nor the pathways involved in this response.

Previous research has shown the ability of resistance exercise to promote changes in vascular function in rats (Faria Tde et al., 2010; Harris et al., 2010). Interestingly, these changes can be produced in blood vessel far from the skeletal muscle used during the exercise, such as mesenteric or caudal vascular beds (Araújo et al., 2013; Faria Tde et al., 2010). Moreover, it is related in the literature that results obtained in mesenteric vascular bed may have physiological relevance

* Corresponding author at: Federal University of Sergipe, Department of Physiology, Cidade Universitária Prof. José Aloísio de Campos, Rosa Elze, Cep: 49100-000, São Cristóvão, Sergipe, Brazil. Tel.: +55 79 21056842.
E-mail address: marcio@infonet.com.br (M.R.V. Santos).

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10.3. APÊNDICE C- Resistance Exercise Restores Endothelial Function and Reduces Blood Pressure in Type 1 Diabetic Rats. Arquivos Brasileiros de Cardiologia (Impresso), p. 1-0, 2014.

Original Article

Resistance Exercise Restores Endothelial Function and Reduces Blood Pressure in Type 1 Diabetic Rats

Marcelo Mendonça Mota[1], Tharciano Luiz Teixeira Braga da Silva[1], Milene Tavares Fontes[1], André Sales Barreto[1], João Eliakim dos Santos Araújo[1], Antônio Cesar Cabral de Oliveira[2], Rogério Brandão Wichi[2], Márcio Roberto Viana Santos[1]

Departamento de Fisiologia - Universidade Federal de Sergipe (UFS)[1]; Departamento de Educação Física - UFS[2], São Cristóvão, SE – Brazil

Abstract

Background: Resistance exercise effects on cardiovascular parameters are not consistent.

Objectives: The effects of resistance exercise on changes in blood glucose, blood pressure and vascular reactivity were evaluated in diabetic rats.

Methods: Wistar rats were divided into three groups: control group (n = 8); sedentary diabetic (n = 8); and trained diabetic (n = 8). Resistance exercise was carried out in a squat device for rats and consisted of three sets of ten repetitions with an intensity of 50%, three times per week, for eight weeks. Changes in vascular reactivity were evaluated in superior mesenteric artery rings.

Results: A significant reduction in the maximum response of acetylcholine-induced relaxation was observed in the sedentary diabetic group (78.1 ± 2%) and an increase in the trained diabetic group (95 ± 3%) without changing potency. In the presence of N^G-nitro-L-arginine methyl ester, the acetylcholine-induced relaxation was significantly reduced in the control and trained diabetic groups, but not in the sedentary diabetic group. Furthermore, a significant increase ($p < 0.05$) in mean arterial blood pressure was observed in the sedentary diabetic group (104.9 ± 5 to 126.7 ± 5 mmHg) as compared to that in the control group. However, the trained diabetic group showed a significant decrease ($p < 0.05$) in the mean arterial blood pressure levels (126.7 ± 5 to 105.1 ± 4 mmHg) as compared to the sedentary diabetic group.

Conclusions: Resistance exercise could restore endothelial function and prevent an increase in arterial blood pressure in type 1 diabetic rats. (Arq Bras Cardiol. 2014; 103(1):25-32)

Keywords: Rats; Exercise; Physical endurance; Endothelium, vascular / physiology; Arterial Pressure / physiology; Diabetes.

Introduction

Diabetes mellitus is a heterogeneous group of metabolic disorders that have in common hyperglycemia associated with secondary cardiovascular system complications[1,2]. Increased blood glucose levels are associated with *in vivo* and *in vitro* endothelial dysfunction[3,4]. Endothelial dysfunction is a systemic phenomenon related to an unbalance in the endothelial production of mediators that regulate vascular tone; it contributes partially to increase arterial blood pressure levels[5]. The endothelial dysfunction in type 1 diabetes mellitus can be considered an early marker of cardiovascular disease[6].

Several factors, such as hyperlipidemia, insulin resistance, hyperglycemia and hypertension, can explain the endothelial dysfunction in type 1 diabetes mellitus[7]. Resistance exercise has been reported to contribute to prevent/treat pathologies that affect the metabolism and cardiovascular function[8-10]. Resistance exercise has proved to have an important therapeutic potential by promoting skeletal muscle mass gain, increased insulin sensitivity and blood glucose reduction in diabetic rats[8,11]. Aerobic exercise also have those effects[11,12].

Some studies have suggested that aerobic exercise is effective to treat endothelial dysfunction in diabetes[13-15]. However, little is known about the chronic effects of resistance exercise on the arterial blood pressure and endothelial function of type 1 diabetic rats. We raised the hypothesis that long-term resistance exercise can minimize the deleterious effects on the cardiovascular system and on the metabolic control of type 1 diabetes mellitus-induced animals. Thus, this study aimed at assessing the chronic effects of resistance exercise on blood glucose changes, vascular reactivity and arterial blood pressure of diabetic rats.

Methods

Animals and experimental delineation

Male Wistar rats (*Rattus norvegicus*), aged 3 months, weighing 250-300 g, were used in all experiments. They were

Mailing Address: Marcio Roberto Viana Santos •
Departamento de Fisiologia, Universidade Federal de Sergipe, Avenida Marechal Rondon, s/n, Rosa Elze. Postal Code 49100-000, São Cristóvão, SE – Brazil
E-mail: marciorvsantos@bol.com.br, marcio@infonet.com.br
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10.4. APÊNDICE D- Prêmio ABC de Publicação Científica. Categoria: Melhor Artigo Original 2014. Resistance Exercise Restores Endothelial Function and Reduces Blood Pressure in Type 1 Diabetic Rats. Arquivos Brasileiros de Cardiologia (Impresso), p. 1-0, 2014.


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Certificado

Melhor Artigo Original (2014)

Exercício Resistido Restaura a Função Endotelial e Reduz a Pressão Arterial de Ratos Diabéticos Tipo 1

Certificado concedido a

Marcelo Mendonça Mota, Tharciano Luiz Teixeira Braga da Silva, Milene Tavares Fontes, André Sales Barreto, João Eliakim dos Santos Araújo, Antônio Cesar Cabral de Oliveira, Rogério Brandão Wichi, Márcio Roberto Viana Santos

Em recebimento do X Prêmio ABC de Publicação Científica

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Dr. Luiz Felipe P. Moreira
Editor-Chefe dos Arquivos Brasileiros de Cardiologia

10.5. APÊNDICE E- Treinamento aeróbio previne alterações na vasodilatação dependente do endotélio em ratos diabéticos. Revista da Educação Física (UEM. Impresso), v. 24, p. 423-432, 2013.

DOI: 10.4025/reveducfis.v24.3.18208

TREINAMENTO AERÓBIO PREVINE ALTERAÇÕES NA VASODILATAÇÃO DEPENDENTE DO ENDOTÉLIO EM RATOS DIABÉTICOS

AEROBIC TRAINING PREVENTS CHANGES IN ENDOTHELIUM-DEPENDENT VASODILATION OF DIABETIC RATS

Marcelo Mendonça Mota*
Tharciano Luiz Teixeira Braga da Silva*
André Sales Barreto*
Milene Tavares Fontes**
Antonio Cesar Cabral de Oliveira***
Márcio Roberto Viana dos Santos****

RESUMO
O objetivo do presente estudo é verificar os efeitos do treinamento aeróbio sobre a reatividade vascular em artéria mesentérica de ratos diabéticos. Ratos Wistar foram divididos em três grupos: controle sedentário (CS), diabético sedentário (DS) e diabético treinado (DT). Alterações na reatividade vascular foram avaliadas após a última sessão de treinamento, por meio da obtenção de curvas concentração-resposta. Os testes *t* de *Student* ou análise de variância (ANOVA) de duas-vias, seguida do pós-teste de Bonferroni, foram realizados para avaliar a significância das diferenças entre as médias. Foi observada uma redução dos relaxamentos induzidos por acetilcolina no grupo DS (79,7 ± 3,0 %), quando comparado ao CS (98,8 ± 3,0) e uma manutenção dos valores normais no grupo DT (100,1 ± 5,3 %). Os resultados sugerem que o treinamento aeróbio é capaz de proporcionar efeitos benéficos na função vascular de ratos diabéticos.

Palavras-chave: Diabetes mellitus. Atividade física. Endotélio vascular.

INTRODUÇÃO

Diabetes mellitus (DM) é uma desordem metabólica crônica caracterizada não apenas por alterações no metabolismo dos carboidratos, das proteínas e dos lipídios, como também causa a disfunção endotelial (DE) (NACCI; TARQUINIO; MONTAGNANI, 2009; VAN DEN OEVER et al., 2010). Do ponto de vista prático, a DE é definida como uma alteração do relaxamento vascular dependente do endotélio (BAHIA et al., 2006). O desenvolvimento da DE tem sido repetidamente demonstrado em vários leitos vasculares, tanto em humanos, quanto em animais induzidos quimicamente ao DM (JOHNSTONE et al., 1993).

A DE tem sido considerada como um evento precoce na patogênese das complicações vasculares do Diabetes mellitus tipo 1 (DM1) (DE VRIESE et al., 2000). Ela reflete a presença de um fenótipo propenso à aterogênese e pode, dessa forma, servir de marcador de risco para aterosclerose. Além disso, tem sido demonstrado que a DE constitui-se em

** Doutorando. Núcleo de Pós-Graduação em Medicina da Universidade Federal de Sergipe, Aracaju SE, Brasil.
* Mestre.Núcleo de Pós-Graduação em Medicina da Universidade Federal de Sergipe, Aracaju-SE, Brasil.
*** Doutor. Departamento de Educação Física da Universidade Federal de Sergipe, São Cristóvão-SE, Brasil.
**** Doutor. Departamento de Fisiologia da Universidade Federal de Sergipe, São Cristóvão-SE, Brasil.

10.6. APÊNDICE F- Suplementação com L-arginina associada ao exercício resistido melhora a força muscular e impede o aumento da glicemia de ratos diabéticos. Revista Ciências Médicas e Biológicas, v. 12, p. 89-93, 2013.

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Suplementação com L-arginina associada ao exercício resistido melhora a força muscular e impede o aumento da glicemia de ratos diabéticos

L-arginine Supplementation associated with resistance exercise improves muscle strength and prevents the increase in blood glucose in diabetic rats

Tharciano Luiz Teixeira Braga da Silva[1], Marcelo Mendonça Mota[1], Milene Tavares Fontes[2], Ana Paula dos Santos Soares[3], André Sales Barreto[4], Anderson Carlos Marçal [5], Márcio Roberto Viana Santos[6]

[1]Professor de Educação Física, Doutorando do Núcleo de Pós-Graduação em Medicina da UFS, [2] Professora de Educação Física, Mestranda do Núcleo de Pós-Graduação em Medicina da UFS, [3]Professora de Educação Física pela UFS, [4]Fisioterapeuta, Professor Assistente do Núcleo de Educação em Saúde da UFS, [5]Licenciado em Ciências, Professor Adjunto de Anatomia Humana da UFS, [6] Biólogo, Professor Adjunto do Departamento de Fisiologia da UFS.

Resumo
Introdução: Diversas terapêuticas têm sido empregadas no controle do diabetes. **Objetivo:** O objetivo deste estudo foi avaliar os efeitos da suplementação com L-arginina e do exercício resistido, isolado ou combinado sobre a massa corporal, glicemia e a força muscular de ratos diabéticos. **Metodologia:** Ratos Wistar foram divididos em 6 grupos: Controle (CON, n = 5), estimulado eletricamente (EE, n = 5), diabético sedentário (DS, n = 5), diabético L-arginina (DL-Arg, n = 5), diabético treinado (DT, n = 5) e diabético treinado + L-arginina (DT + L-Arg, n = 5). O diabetes foi induzido através da administração de aloxano na dose única de 40 mg/kg, i.v., duas semanas antes do início dos protocolos. Foi avaliada a massa corporal, glicemia e a força muscular no início, a cada duas semanas e no final das 6 semanas dos procedimentos experimentais. **Resultados:** No início do estudo, o DS apresentou um aumento significativo ($p < 0,001$) da glicemia quando comparado com o CON. Após as 6 semanas de estudo os animais do grupo DT e DT + L-Arg obtiveram um aumento significativo ($p < 0,01$ e $p < 0,001$; respectivamente) nos níveis de força quando comparado com o DS. Os animais DT + L-Arg apresentaram uma redução significativa ($p < 0,001$) da glicemia plasmática ao longo do tratamento quando comparado com o DS. **Conclusão:** A suplementação com L-arginina associada ao exercício resistido aumenta a força muscular e promove um equilíbrio metabólico em animais diabéticos.
Palavras-chave: Diabetes Mellitus. Arginina. Treinamento de resistência.

Abstract
Introduction: *Several therapies have been used to control diabetes.* ***Objective:*** *The aim of our study was evaluate the effects of L-arginine supplementation and resistance exercise, alone or in combination on body weight, blood glucose and muscle strength in diabetic rats.* ***Methodology:*** *Wistar rats were divided into 6 groups: control (CON, n = 5), electrically stimulated (ES, n = 5), sedentary diabetic (SD, n = 5), diabetic L-arginine (DL-Arg, n = 5), trained diabetic (TD, n = 5) and trained diabetic + L-arginine (TD + L-Arg, n = 5). Diabetes was induced by administration of alloxan in a single dose of 40 mg / kg, iv, two weeks before the start of the protocols. Was evaluated the body mass, blood glucose and muscle strength at the beginning of the experiment, every two weeks and at the end of the experimental procedures.* ***Results:*** *At baseline, the DS showed a significant increase ($p < 0.001$) glucose when compared with the CON. After 6 weeks of study animals from group TD and TD + L-Arg had a significant increase ($p < 0.01$ and $p < 0.001$, respectively) at muscle strength. The animals TD + L-Arg presented a significant reduction ($p < 0.001$), plasma glucose during the treatment group compared to SD.* ***Conclusions:*** *L-arginine Supplementation associated with resistance exercise increases muscle strength and promotes a metabolic balance in diabetic animals.*
Keywords: *Diabetes mellitus. Arginine. Resistance training.*

INTRODUÇÃO

O diabetes mellitus (DM) pode ser definido como um grupo heterogêneo de distúrbios metabólicos caracterizados pela hiperglicemia, causado por uma disfunção na secreção da insulina ou na ação desta, ou por ambas as coisas (SHI et al., 2006; ADA, 2008). Existem dois tipos principais de DM, o DM tipo 1 (DM1) onde os portadores são dependentes do uso da insulina, e o DM tipo 2 (DM2), em que os pacientes apresentam uma concentração plasmática do hormônio mas este é ineficaz (SBD, 2007). Em condições crônicas o DM1 descompensado resulta em disfunção, lesão e, em última instância, insuficiência de vários órgãos (ADA, 2008).

Dentre as diversas terapêuticas empregadas na melhora do DM, tem sido indicada a prevenção primária que inclui mudanças na dieta alimentar e a prática de

Correspondência / Correspondence: Márcio Roberto Viana dos Santos. Universidade Federal de Sergipe, Centro de Ciências Biológicas e da Saúde. Campus Universitário, S/N. Cidade Universitária. CEP: 49100-000 - Aracaju, SE – Brasil. Telefone: (79) 21056842. http://www.ufs.br

10.7. APÊNDICE G- Acute effects of the resistance exercise over the endothelium-dependent relaxation in the mesenteric artery of healthy rats. Indian Journal of Experimental Biology, 2014.

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Acute effects of the resistance exercise over the endothelium-dependent relaxation in the mesenteric artery of healthy rats

T.L.B.T. Silva[a], M.T. Fontes[a], M.M. Mota[a], R. B. Wichi[b,*], L. R. Bonjardim[c], M.R.V. Santos[a]

Abstract

The present study evaluated the effect of a session of resistance exercise over the endothelium-dependent relaxation in the mesenteric artery of healthy rats. The animals were divided into three groups: control (CT), electrically stimulated (ES) and resistance exercise (RE). Immediately after the resistance exercise, the animals were sacrificed and the mesenteric artery rings were suspended on an isometric force transducer. Concentration-response curves for acetylcholine (ACh) were developed in the control condition and in the presence of L-NAME (NOS inhibitor), L-NAME + INDO (COX inhibitor) or L-NAME + INDO + TEA (inhibitor of K^+ channels). Animals submitted to a resistance exercise session showed a higher sensitivity to vasodilation induced by ACh compared to the CT group. The NOS inhibition reduced the ACh-induced relaxation in the RE group when compared to the CT group. When added to the L-NAME + INDO bath, the relaxations in the RE group presented a smaller inhibitory response when compared to the CT group. In the presence of the three inhibitors, the vasodilator response for ACh was blocked in the RE group when compared to the CT group. Those results suggest that the acute resistance exercise promotes an increase in the ACh-induced endothelium-dependent vasodilatation.

Keywords: exercise, mesenteric artery, insulin, vascular endothelium.

10.8. APÊNDICE H- Efeitos de uma sessão de exercício resistido sobre o músculo liso vascular em artéria mesentérica de ratos hipertensos induzidos por L-NAME. Arquivos Brasileiros de Cardiologia, 2014.

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Efeitos de uma sessão de exercício resistido sobre o músculo liso vascular em artéria mesentérica de ratos hipertensos induzidos por L-NAME.

Silva, T.L.B.T.[a], Mota, M.M.[a], Fontes, M.T.[a], Araujo, J. E. S.[a], Cunha, P. S.[a], Carvalho, V. O.[b], Bonjardim, L. R.[c], Santos, M.R.V.[a,*]

Resumo

Fundamento: A hipertensão é um problema de saúde pública e que aumenta a incidência das doenças cardiovasculares.

Objetivo: Avaliar os efeitos agudos do exercício resistido sobre os mecanismos contráteis e relaxantes do músculo liso vascular em artéria mesentérica de ratos hipertensos induzidos por L-NAME.

Métodos: Ratos Wistar foram divididos em três grupos: controle (C), Hipertenso (H) e Hipertenso treinado (HT). A hipertensão foi induzida pela administração de 20 mg/kg de NG-nitro L-arginina metil éster (L-NAME) durante 7 dias antes dos protocolos experimentais. O protocolo de exercício resistido consistiu em 10 séries de 10 repetições e intensidade de 40% de uma repetição máxima. A reatividade do músculo liso vascular foi avaliada através de curvas concentração-resposta para a fenilefrina (FEN), cloreto de potássio (KCl) e nitroprussiato de sódio (NPS).

Resultados: Os ratos tratados com L-NAME apresentaram um aumento ($p<0,001$) da pressão arterial sistólica (PAS), pressão arterial diastólica (PAD) e pressão arterial média (PAM) quando comparado ao período inicial da indução. Não foi observada diferença na sensibilidade da FEN entre os grupos H e HT. O exercício resistido agudo reduziu ($p<0,001$) a resposta contrátil induzida pelo KCl nas concentrações de 40 e 60 mM do grupo HT quando comparado ao grupo H. Foi observado uma maior ($p<0,01$) sensibilidade do músculo liso ao NPS no grupo HT quando comparado ao grupo H.

Conclusão: O exercício resistido agudo reduz das respostas contráteis induzidas pelo KCl, além de aumentar a sensibilidade do músculo liso ao NO em artéria mesentérica de ratos hipertensos.

Palavras-chave: Hipertensão; Exercício; vasodilatação.