TREINAMENTO FÍSICO E INSUFICIÊNCIA CARDÍACA: BIOMARCADORES E VARIÁVEIS FUNCIONAIS

Tese de Doutorado

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SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

ACCF: American College of Cardiology Foundation

AHA: American Heart Association

BNP: Peptídeo Natriurético B

IC: Insuficiência Cardíaca

ICFEp: Insuficiência Cardíaca com Fração de Ejeção Preservada

ICFEr: Insuficiência Cardíaca com Fração de Ejeção Reduzida

IGF1: Fator de crescimento semelhante à insulina 1

IL: interleucina

VE/VCO_2: Relação Ventilação-Produção de Dióxido de Carbono

VO_2: Consumo de Oxigênio

NFκB: Fator Nuclear Kappa B

NT-proBNP: Fragmento N-Terminal do Peptídeo B

PCR: Proteína C-Reativa

SRAA: Sistema Renina-Angiotensina-Aldosterona

TNF-α: Fator de Necrose Tumoral-alfa

RESUMO

Objetivo: Avaliar os efeitos do treinamento físico sobre biomarcadores e variáveis funcionais em pacientes com insuficiência cardíaca (IC). Métodos: A revisão sistemática e meta-análise incluiu ensaios clínicos randomizados (ECR) de indivíduos com IC que realizaram treinamento físico com os desfechos primários peptídeo natriurético B e fragmento N-terminal do peptídeo natriurético B. No ensaio clínico randomizado indivíduos com IC realizaram treinamento funcional ou de força, 3 vezes/semana, 12 semanas. Resultados: A revisão sistemática demonstrou associação entre o treinamento físico e peptídeos natriuréticos. O ECR demonstrou que treinamento funcional e de força melhoram o VO_2 de pico e a qualidade de vida. Conclusões: O treinamento físico em pacientes com IC está associado a efeitos benéficos sobre os peptídeos natriuréticos e biomarcadores inflamatórios, uma vez que todos foram reduzidos pela intervenção. O treinamento funcional e de força são igualmente seguros e eficazes para melhorar a capacidade funcional, qualidade de vida e funcionalidade de indivíduos com IC.

Palavras-chave: Insuficiência cardíaca. Treinamento funcional. Capacidade cardiopulmonar. Qualidade de vida. Exercício. Peptídeos natriuréticos. Biomarcadores inflamatórios. Troponinas cardíacas.

ABSTRACT

Objective: To evaluate the effects of physical training on biomarkers and functional variables in patients with heart failure (HF). Methods: The systematic review and meta-analysis included randomized clinical trials (RCT) of individuals with HF who underwent physical training with the primary endpoints of natriuretic peptide B and N-terminal fragment of natriuretic peptide B. In the randomized clinical trial, subjects with HF underwent functional training or strength training, 3 times/week, 12 weeks. Results: The systematic review showed an association between physical training and natriuretic peptides. The RCT showed that functional and strength training improve peak VO_2 and quality of life. Conclusions: Physical training in patients with HF is associated with beneficial effects on natriuretic peptides and inflammatory biomarkers, since all were reduced by the intervention. Functional and strength training are equally safe and

effective for improving functional capacity, quality of life, and functionality for individuals with HF.

Keywords: Heart Failure. Functional training. Cardiopulmonary capacity. Quality of life. Exercise. Natriuretic peptides. Inflammatory biomarkers. Cardiac troponins.

REVISÃO DA LITERATURA

A insuficiência cardíaca (IC) é um importante problema de saúde pública, afetando quase 20 milhões de pessoas em todo o mundo, com um aumento projetado de 25% na sua prevalência em 2030[1]. Considerando a idade, a prevalência de IC dobra a cada década de vida, sendo inferior a 1% para indivíduos abaixo de 40 anos e maior que 10% para aqueles acima de 80 anos[2]. Declínio na mortalidade por IC tem sido documentado e parece estar relacionado às estratégias na identificação de fatores de risco para o desenvolvimento da doença, bem como à implementação de terapia farmacológica, revascularização do miocárdio e de ressincronização cardíaca[2]. Entretanto, a taxa de mortalidade por IC após cinco anos do seu diagnóstico permanece elevada, aproximadamente 50%, com maior prevalência em idades mais avançadas[3].

Definida como uma síndrome clínica complexa, a IC constitui-se na incapacidade do coração em aumentar o débito cardíaco a um nível compatível com as necessidades metabólicas teciduais, ou o faz às custas de uma elevada pressão de enchimento ventricular[4]. A IC resulta de dano cardíaco estrutural ou funcional, que conduz a inadequado enchimento e/ou ejeção do ventrículo esquerdo[5]. Adaptações neuro-humorais, tais como ativação dos sistemas simpático e renina-angiotensina-aldosterona, aumento do hormônio antidiurético e redução da atividade parassimpática estão presentes na IC[1].

A persistente hiperatividade simpática e ativação da cascata neuro-humoral resultam em hipertrofia e remodelamento do ventrículo esquerdo, edema pulmonar e vasoconstrição excessiva, podendo levar à descompensação cardíaca[6, 7]. Na tentativa de neutralizar a vasoconstrição excessiva, outros sistemas são requisitados, ocorrendo a liberação de peptídeos natriuréticos e de moléculas vasodilatadoras, como as prostaglandinas e o óxido nítrico[7]. A ineficiência destes sistemas, e a ação no próprio coração de proteínas liberadas pelo sistema neuro-humoral (norepinefrina, angiotensina II, endotelina e aldosterona), contribuem para o caráter progressivo da doença, uma vez que mais estimulação adrenérgica cardíaca será necessária a fim de estabilizar ou mesmo aumentar o desempenho do miocárdio[7, 8]. Associado a isto, a persistência da inflamação além da fase inicial de reparo pode posteriormente se estender pelo miocárdio, desempenhando papel importante no remodelamento ventricular adverso e piora da função cardíaca[9], além de contribuir para as alterações periféricas da IC, como aquelas encontradas no músculo esquelético[10].

A dificuldade do coração em atender às demandas teciduais resulta em sintomas de dispneia e intolerância aos esforços e, diferentemente do que se poderia pensar, dados da literatura demonstram uma fraca relação da fração de ejeção do ventrículo esquerdo em repouso com a tolerância ao exercício[11]. Por outro lado, anormalidades nos músculos esqueléticos contribuem de forma substancial para a limitada capacidade funcional presente nos pacientes com IC[12]. Estas anormalidades caracterizam a miopatia do músculo esquelético induzida pela IC e compreendem principalmente a inversão no tipo de fibra muscular, com menor porcentagem de fibras de contração lenta tipo I (oxidativas) e maior porcentagem de fibras de contração rápida tipo II (glicolíticas); redução na atividade de enzimas oxidativas, em especial das enzimas mitocondriais e as que envolvem a beta oxidação de ácidos graxos; acúmulo precoce de ácido lático; e atrofia muscular[13, 14]. A disfunção endotelial contribui para a miopatia do músculo esquelético, reduzindo a oferta de oxigênio durante episódios de maior demanda, o que resulta em fadiga e tolerância diminuída ao exercício[15].

A intolerância ao exercício é definida como a capacidade reduzida de realizar atividades que envolvam grandes grupos musculares[4, 16], e acompanhada de dispneia e fadiga, constitui-se no principal sintoma da IC[11]. Na hipótese muscular, inicialmente proposta por Piepoli et al[17], as anormalidades encontradas no músculo esquelético, associadas ao acúmulo de metabólitos como íons hidrogênio, prostaglandinas e bradicinina, aumentam a atividade ergorreflexa durante o exercício, levando a uma resposta ventilatória, hemodinâmica e simpática exagerada. A consequente vasoconstrição e aumento da pós-carga piora ainda mais a função ventricular, que contribui para a miopatia do músculo esquelético e mais intolerância ao exercício, gerando um ciclo vicioso[18].

Posteriormente, evidências demonstraram que níveis altos de inflamação também contribuem para as alterações nos músculos esqueléticos e a interação entre a ativação neuro-humoral e o sistema inflamatório, no modelo imunohumoral, está presente na sua patogênese[19]. A ativação simpática mobiliza monócitos da medula óssea potencialmente por meio de mecanismo β3-adrenérgico, enquanto a sinalização parassimpática por meio de receptores nicotínicos de acetilcolina é um importante regulador negativo das respostas imunes inatas pró-inflamatórias[20]. O aumento da angiotensina II desencadeia a geração de espécies reativas de oxigênio por meio da estimulação direta da NADPH oxidase, ativa a expressão do fator de transcrição pró-inflamatório NFκB (Fator Nuclear Kappa B) em miócitos do músculo esquelético e suprime a sinalização de IGF1 (Fator de crescimento

semelhante à insulina 1), um fator importante no desenvolvimento dos músculos esqueléticos[10].

Dispneia e intolerância ao exercício são sintomas importantes na IC, presentes já nos estágios iniciais da doença e progredindo com a gravidade da disfunção cardíaca[21]. A tolerância diminuída ao exercício está associada a pior qualidade de vida e ao aumento da mortalidade[11]. Além do tratamento farmacológico[5, 22], intervenções não farmacológicas como o uso de cardiodesfibrilador implantável, terapia de ressincronização cardíaca e treinamento físico são importantes para estes pacientes.

EXERCÍCIO FÍSICO NA IC

O *American College of Cardiology Foundation* (ACCF) e a *American Heart Association* (AHA) atribuem classe I e nível de evidência A ao treinamento físico no que concerne à segurança e à efetividade desta intervenção para melhora do *status* funcional de pacientes com IC estável[5]. O treinamento físico tem sido enfatizado no tratamento de pacientes com IC por reverter parcialmente as alterações centrais e periféricas presentes na doença.

Os efeitos positivos do exercício físico regular foram descritos quanto à capacidade aeróbia[23, 24], equilíbrio simpatovagal[23], qualidade de vida e morbimortalidade[24] de pacientes com IC.

Pacientes com IC, mesmo quando estáveis e compensados, apresentam declínio na sua capacidade funcional manifestando tolerância diminuída ao exercício[25]. O consumo de oxigênio (VO_2) é um importante preditor para a doença, embora o seu aumento não apresente relação com a melhora da fração de ejeção do ventrículo esquerdo. Por outro lado, o VO_2 apresenta correlação positiva com a massa muscular de quadríceps, circunferência média do braço e área muscular, sugerindo que a atrofia dos músculos periféricos contribui para a intolerância ao exercício em pacientes com IC[26; 27]. Já a perda de massa muscular está fortemente associada à redução do VO_2 de pico [28, 29]. De fato, a perda de força e massa musculares, conhecida como sarcopenia, apresenta elevada prevalência nesta população[30] e constitui-se em importante determinante da independência funcional, taxa de internação hospitalar e qualidade de vida[31, 32]. Pacientes com IC apresentam redução de cerca de 30% na capacidade de realizar atividades de vida diária, quando comparados a indivíduos saudáveis, e isso tem sido atribuído à massa muscular reduzida e à menor capacidade aeróbia[33].

Bellardineli et al[24] demonstraram aumento no VO_2 de pico e na qualidade de vida de pacientes com ICFEr após oito semanas de treinamento aeróbio de intensidade moderada, comparado ao grupo controle de cuidados usuais. Os escores de qualidade de vida mantiveram-se superiores nos pacientes treinados em comparação ao grupo controle, mesmo após o período de manutenção do estudo. Além disso, houve forte correlação positiva entre a qualidade de vida e o VO_2 de pico. Os mesmos autores[34] avaliaram os efeitos do exercício em pacientes com ICFEr após 10 anos de treinamento aeróbio. Com uma adesão de 88% ao programa de exercícios, os pacientes treinados tiveram aumento do VO_2 de pico e da qualidade de vida que mantiveram-se mais elevados em comparação aos controles até o final do estudo. Também em pacientes com ICFEr, o estudo HF-ACTION (*Heart Failure and a Controlled Trial Investigating Outcomes of Exercise Training*)[35] mostrou aumento, embora modesto, do VO_2 de pico nos indivíduos treinados versus controles, após 12 semanas de treinamento aeróbio.

Em recente revisão sistemática e meta-análise[36] foi demonstrado o efeito positivo do treinamento aeróbio no aumento do VO_2 de pico (6 estudos; 314 pacientes) e da qualidade de vida (5 estudos, 256 pacientes) de pacientes com ICFEp, comparado com controles sedentários. Por outo lado, o treinamento de força também pode apresentar efeitos favoráveis sobre a capacidade aeróbia e qualidade de vida de pacientes com IC. A revisão sistemática e meta-análise de Jewiss et al[37] (27 estudos, 2.321 pacientes) demonstrou aumento do VO_2 de pico e da distância percorrida no teste da caminhada de seis minutos em pacientes com IC que realizaram treinamento de força isolado ou combinado ao treinamento aeróbio, versus controles. Os escores de qualidade de vida foram maiores somente para o treinamento combinado, comparado ao grupo controle.

A sarcopenia (perda de massa e função musculares) está presente na IC, sendo um forte preditor para fragilidade, incapacidade e mortalidade[32]. A velocidade da marcha e a força de preensão palmar são variáveis importantes que auxiliam na avaliação da disfunção dos músculos esqueléticos[38]. O treinamento físico, especialmente com exercícios de força, tem sido indicado para o tratamento da sarcopenia[32]. A revisão sistemática e meta-análise de Giuliano et al[39] avaliou os efeitos do treinamento de força sobre a qualidade de vida, força muscular e capacidade aeróbia em pacientes com IC crônica. Para o desfecho de força muscular, a análise de quatro estudos demonstrou aumento na diferença média de uma repetição máxima no *leg press*, em pacientes treinados versus controles sedentários. A capacidade aeróbia e a qualidade de vida também foram positivamente influenciadas pelo treinamento de força.

A miopatia do músculo esquelético não está restrita à periferia. A fraqueza dos músculos inspiratórios é prevalente na IC e contribui para um pior prognóstico nestes pacientes[40]. A revisão sistemática de Wu et al[41] demonstrou, por meio da análise de seis estudos, o aumento da pressão inspiratória máxima em pacientes que realizaram treinamento muscular inspiratório versus controles não-treinados. As análises também mostraram que o treinamento muscular inspiratório tem efeitos positivos sobre a relação ventilação-produção de dióxido de carbono (VE/VCO_2 *slope*) e dispneia, reduzindo seus valores.

À luz das evidências científicas, portanto, os benefícios do treinamento físico estão associados às respostas fisiológicas por ele induzidas no músculo esquelético, no sistema respiratório e cardiovascular. Considerando a especificidade do treinamento, três principais modalidades de treinamento físico têm sido propostas no cenário da IC, com diferentes combinações: aeróbio, resistido (ou de força) e respiratório[42].

O processo fisiopatológico da IC envolve a liberação de inúmeras substâncias na circulação que podem ser usadas como biomarcadores[43], e estratégias terapêuticas que combinem múltiplos marcadores podem se provar benéficas em guiar o ajuste terapêutico. A literatura científica busca demonstrar o efeito do treinamento físico sobre diferentes biomarcadores em pacientes com IC, em especial peptídeos natriuréticos e marcadores inflamatórios.

Em um sub-estudo[44] do HF-ACTION, o NT-proBNP demonstrou ser um forte preditor para o VO_2 de pico, apresentando correlação inversa com a capacidade de exercício em pacientes com IC, embora sem diferença na sua concentração plasmática após três meses de treinamento[16]. Já o estudo de Giallauria et al[45] mostrou valores menores de NT-proBNP após três meses de treinamento aeróbio após infarto agudo do miocárdio, além de correlação inversa entre o biomarcador e o VO_2 de pico. Também revisões sistemáticas têm apontado para o efeito positivo do treinamento físico sobre a redução nas concentrações de ambos os peptídeos, BNP[46-48] e NT-proBNP[49], em pacientes com IC.

Embora a literatura venha demonstrando algum efeito do treinamento físico sobre biomarcadores inflamatórios e troponinas cardíacas em pacientes com IC, os resultados são ainda mais conflitantes. Além das concentrações de NT-proBNP, Ahmad et al[16] também avaliou o efeito de 12 semanas de treinamento aeróbio contínuo sobre as concentrações plasmáticas de proteína C-reativa (PCR), em uma coorte de 928 indivíduos com ICFEr, originária do estudo HF-ACTION. Os resultados não demostraram efeito do

treinamento físico sobre este biomarcador. Ao contrário, Abolahari-Shirazi et al[50] encontraram concentrações de PCR reduzidas em pacientes com IC após sete semanas de treinamento aeróbio contínuo, mas não após treinamento combinado. Também no estudo de Aksoy et al[51], a PCR esteve reduzida no grupo de pacientes com IC que realizou treinamento aeróbio contínuo, em comparação ao grupo controle, mas não para aqueles que realizaram treinamento aeróbio intermitente.

Quanto às citocinas inflamatórias, a revisão sistemática de Smart et al[52] demonstrou o efeito do treinamento físico na redução das concentrações plasmáticas de TNF-α em apenas quatro dos 11 estudos incluídos, sendo que um dos estudos avaliou a resposta do TNF-α induzida pela estimulação elétrica funcional. Os resultados para a IL-6 plasmática foram ainda mais limitados. Somente um estudo indicou o efeito positivo do treinamento físico sobre o biomarcador. As interleucinas IL-1ß e IL-10 foram avaliadas em apenas um estudo e não apresentaram alteração o treinamento físico. A heterogeneidade metodológica entre os estudos e as diferentes características clínicas dos pacientes não permitiram aos autores realizar a meta-análise dos dados. Os achados da recente revisão sistemática e meta-análise de Pearson et al[53] também não são tão promissores. Os autores demonstraram pequeno efeito do treinamento físico na redução de TNF-α e IL-6 circulantes em pacientes com IC, mas não sobre a PCR. Após análise de sensibilidade, os resultados favoráveis à IL-6, no entanto, foram atribuídos a um único estudo, comprometendo os achados para este biomarcador.

Estes achados, compilados em revisões sistemáticas[46, 48, 49, 52, 53], sugerem algum efeito benéfico do treinamento físico na redução destes biomarcadores, mais ainda conflitantes, em especial no que concerne aos biomarcadores inflamatórios.

Há ainda poucos estudos avaliando o efeito do treinamento físico sobre as troponinas cardíacas no cenário da IC. No entanto, concentrações elevadas destes biomarcadores são frequentemente encontradas na circulação de pacientes com IC sintomáticos, mesmo na ausência de isquemia miocárdica[5]. Estudos[54, 55] demonstram elevação aguda das concentrações de troponinas induzida pelo exercício também em indivíduos saudáveis. Aengevaeren et al[56] avaliaram as concentrações de troponina I em 725 indivíduos antes e imediatamente após caminhada de longa distância. A elevação da troponina I esteve independentemente associada à mortalidade em geral e a eventos cardiovasculares maiores. Vários questionamentos persistem quanto aos fatores responsáveis por essa elevação, significado clínico e prognóstico. Obokata[57] et al encontraram concentrações mais elevadas de troponina T em indivíduos com ICFEp no

repouso e durante exercício físico agudo de baixa intensidade (20 watts), comparado a controles sem IC. Além disto, a elevação nas concentrações de troponina durante o exercício esteve diretamente correlacionada com menor reserva sistólica e diastólica do ventrículo esquerdo, maior pressão de enchimento ventricular e menor resposta do débito cardíaco ao exercício físico e capacidade aeróbia. Ahmad et al[16] também avaliaram o efeito do exercício físico crônico sobre a troponina cardíaca T em pacientes com IC. Os autores não encontraram associação entre o treinamento físico e alterações nos níveis deste biomarcador, assim como entre a troponina T e o VO_2 de pico.

TREINAMENTO FUNCIONAL

O treinamento de força aumenta a força muscular, a capacidade aeróbia e a independência funcional, bem como a qualidade de vida, reduzindo a morbidade de indivíduos com e sem doença cardiovascular, com menor sobrecarga ao sistema cardiorrespiratório[28], o que pode ser uma estratégia terapêutica segura e confortável para pacientes com IC. No entanto, as atividades de vida diária requerem uma combinação de *endurance* e força, e o treinamento aeróbio não melhora a força do músculo esquelético, enquanto que o treinamento de força tradicional não representa idealmente os movimentos realizados durante as atividades de vida diária.

Neste sentido, o treinamento funcional surge como alternativa de tratamento para pacientes com IC, pois mescla exercícios aeróbios de curta duração com exercícios de força. Além disto, apresenta interface com outras modalidades de treinamento físico, visto que trabalha com a estabilização do *core*, o equivalente ao *power house* do método Pilates. O *core* constitui-se em uma caixa limitada anteriormente pelos músculos abdominais, posteriormente pelos paravertebrais e glúteos, acima pelo diafragma e abaixo pelo assoalho pélvico e quadril. Serve como uma couraça muscular que trabalha como uma unidade para estabilização do corpo. O fortalecimento ou a facilitação destes músculos tem sido utilizada na prevenção e tratamento de alterações musculoesqueléticas, além da melhora na performance de atletas[58].

O fato do músculo diafragma ser ativado durante os exercícios do *core* indica um potencial para esta modalidade de treinamento ser utilizada também como treinamento diafragmático. Strongoli et al[59] demonstraram aumento da pressão transdiafragmática acima de 50% em seis indivíduos saudáveis durante a realização de exercícios fundamentados no *core*. DePalo et al[60] demonstraram aumento na espessura do

diafragma, da pressão transdiafragmática e da pressão inspiratória e expiratória máximas em quatro indivíduos saudáveis que realizaram 16 semanas de treinamento dos músculos abdominais (*sit-ups* e *biceps curls*).

A revisão sistemática de Liu et al[61] (13 ensaios clínicos, 1.139 participantes) avaliou os efeitos do treinamento funcional sobre a força muscular, funcionalidade e atividades de vida diária em indivíduos acima de 60 anos. Quatro estudos demonstraram aumento da força muscular dos indivíduos que realizaram o treinamento funcional juntamente com exercícios de força, em comparação a controles não-treinados. Porém, em comparação com o treinamento de força, os achados não favoreceram o treinamento funcional, quando este foi executado sem a associação com exercícios de força. Estes resultados podem indicar uma superioridade do treinamento de força sobre o treinamento funcional no âmbito da força muscular, mas não sobre a habilidade em executar as atividades de vida diária.

Atualmente, o treinamento funcional vem sendo utilizado em populações de idosos, com o objetivo de minimizar o risco de quedas[62]. O estudo LIFE (*Lifestyle integrated Functional Exercise*)[63] comparou os efeitos de três programas de exercício físico, realizados durante 12 meses: treinamento funcional, treinamento estruturado (exercícios de equilíbrio e força de membros inferiores), e controle (exercícios de flexibilidade) sobre a incidência de quedas em indivíduos acima de 70 anos. Os autores demonstraram uma redução de 31% na ocorrência de quedas nos participantes do treinamento funcional, quando comparados ao grupo controle. Equilíbrio e variáveis funcionais relacionadas às atividades cotidianas, como nível de atividade física, limitação e independência funcional, também foram mais fortemente influenciadas pelo treinamento funcional. O aumento no gasto energético ocorreu para ambos os programas de exercício, mas com tamanho de efeito maior para o treinamento funcional. Ferraz et al[64] avaliaram a capacidade de caminhada de 62 pacientes acima de 60 anos e com doença de Parkinson, randomizados em três diferentes modalidades de exercícios físicos: treinamento funcional, treinamento aeróbio em cicloergômetro e exercícios utilizando jogos de computador (gameterapia). Após oito semanas, as três intervenções mostraram melhora na distância percorrida no teste da caminhada de seis minutos, mas somente a gameterapia obteve aumento na velocidade da marcha, avaliada pelo *gait speed test*. Também houve melhora na força muscular de membros inferiores, avaliada pelo teste de sentar e levantar, bem como na funcionalidade, avaliada pelo questionário *World Health Organization Disability Schedule* 2.0, mas sem diferença entre os grupos.

O treinamento funcional baseia-se na reprodução dos movimentos fundamentais do homem primitivo que são ainda hoje executados no cotidiano do homem moderno, como agachar, avançar, abaixar, puxar, empurrar, levantar e girar[65]. Tem como princípio a especificidade do treinamento, que significa que o treino em uma atividade específica é a melhor maneira de maximizar o desempenho nessa atividade[66]. Seu objetivo primordial é melhorar a capacidade funcional do indivíduo utilizando exercícios que se relacionam com a sua atividade física específica, transferindo seus ganhos de forma efetiva para o seu cotidiano[61, 65], além de utilizar uma intensidade maior de treinamento com sessões de exercícios mais dinâmicas e que podem ser realizadas em circuito.

O treinamento multicomponente se assemelha ao treinamento funcional e pode ser considerado como tal se incluir no seu treino exercícios direcionados à função[61]. Heubel et al[67] avaliaram o efeito de um protocolo de treinamento multicomponente na aptidão funcional e parâmetros glicêmicos de 13 idosos com diabetes mellitus tipo 2. A intervenção incluiu exercícios de força, equilíbrio, coordenação, marcha, agilidade e propriocepção. Após 16 semanas de treinamento houve aumento no número de repetições do teste de flexão de braços, na medida do teste de sentar e alcançar, na distância percorrida no teste da caminhada dos seis minutos e na redução da hemoglobina glicada. No entanto, os autores não demonstraram melhora da força muscular de membros inferiores, avaliada pelo teste da cadeira, provavelmente por um menor estímulo dado a esses segmentos durante o treinamento.

Com base nestas informações, é possível que o treinamento funcional possa ter ganhos em outros desfechos como a capacidade cardiopulmonar, força muscular inspiratória e qualidade de vida constituindo-se em uma nova modalidade de treinamento para populações especiais, como na IC.

JUSTIFICATIVA E OBJETIVOS

O treinamento físico tem sido enfatizado no tratamento de pacientes com IC por reverter parcialmente as alterações centrais e periféricas presentes na doença, o que pode traduzir-se em melhora da capacidade cardiopulmonar e qualidade de vida. Uma vez que estudos prévios mostraram estes benefícios em pacientes com IC submetidos ao treinamento de força, isoladamente e em associação ao treinamento aeróbio, o treinamento funcional também pode ser efetivo, e até mesmo apresentar superioridade no alcance dos benefícios. No que diz respeito aos efeitos do treinamento físico sobre diferentes biomarcadores da IC, a literatura ainda apresenta lacunas. Estes marcadores fornecem informações importantes sobre a fisiopatologia da doença, além de auxiliar no diagnóstico, estratificação de risco e manejo dos pacientes e, portanto, assumem papel estratégico como alvo terapêutico.

OBJETIVO GERAL

Avaliar os efeitos do treinamento físico sobre biomarcadores e variáveis funcionais em pacientes com insuficiência cardíaca.

OBJETIVOS ESPECÍFICOS

1. Avaliar, por meio de uma revisão sistemática e meta-análise, o efeito do treinamento físico em diferentes biomarcadores: peptídeos natriuréticos, citocinas inflamatórias e troponinas cardíacas, em pacientes com IC.

2. Avaliar os efeitos do treinamento funcional sobre a capacidade cardiopulmonar e qualidade de vida de pacientes com IC, comparando-o ao treinamento de força, mediante um ensaio clínico randomizado.

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ARTIGO 1

Effect of physical training on natriuretic peptides and biomarkers of inflammation in patients with heart failure: systematic review and meta-analysis

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ABSTRACT

Aims: To perform a systematic review and meta-analysis to assess the impact of physical training on HF biomarkers, such as B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP), cardiac troponins and biomarkers of inflammation.

Methods and results: A systematic electronic literature search was conducted in PubMed, Embase, CINAHL, SPORTDiscus and the Cochrane Library [Cochrane Database of Systematic Reviews, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register] to identify randomized clinical trials reporting associations between natriuretic peptides, cardiac troponins and inflammation, and HF patients who had undergone any formal physical training intervention. Thirty-three trials were included in the final meta-analysis. Physical training was associated with decreased BNP (-62.2 pg/ml, 95% CI -116.8 to -7.6, $p = 0.030$; $I^2 = 67\%$) and NT-proBNP (-182.4 pg/ml, 95% CI -298.2 to -66.5, $p = 0.002$; $I^2 = 72\%$) in HF patients. Physical training was also associated with decreased C-reactive protein (-0.18 mg/dl, 95% CI -0.21 to -0.15, $p < 0.01$; $I^2 = 0\%$), tumor necrosis factor α (-0.76 pg/ml, 95% CI -1.43 to -0.09, $p = 0.030$; $I^2 = 56\%$), interleukin 1ß (-0.24 pg/ml, 95% CI -0.38 to -0.09, $p < 0.01$; $I^2 = 6\%$), and interleukin 6 (-0.93 pg/ml, 95% CI -1.82 to -0.05, $p = 0.040$; $I^2 = 59\%$).

Conclusion: Physical training in HF patients is associated with beneficial effects on natriuretic peptides and biomarkers of inflammation, since they were all reduced by the intervention. **Systematic review registration number:** CRD42020191215

Keywords: Heart Failure. Exercise. Natriuretic peptides. Cardiac troponins. Inflammatory biomarkers.

INTRODUCTION

Heart failure (HF) is a complex syndrome[1] with a complex interplay among factors and a poor prognosis[2]. Several biomarkers appear to provide information about the pathogenesis of HF, identify at-risk individuals, and facilitate risk stratification, diagnosis, and therapy monitoring[1]. Some of these biomarkers indicate myocyte stress, such as B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)[2], while others indicate inflammation, such as C-reactive protein (CRP), tumor necrosis factor α (TNF-α), and interleukins (IL) IL-1ß, IL-6 and IL-18. Still others, such as cardiac-specific troponins I and T, indicate myocyte injury[2; 3].

Therapeutic interventions for HF, such as medications, are known to decrease BNPs[4], and inflammatory markers[5]. However, physical training has been reported to attenuate not only neurohormonal stimulation, but natriuretic peptide overexpression and the production of proinflammatory cytokines in chronic HF[6]. However, the impact of physical training interventions on these biomarkers is still poorly explored.

A systematic review investigated the effect of exercise therapy on BNP and NT-proBNP in patients with HF, showing that conventional physical training had a positive influence on these biomarkers, i.e. lower values of both peptides after interventions[7]. However, this study included not only randomized clinical trials (RCTs), but non-RCTs and cohorts with control groups. More recently, a systematic review including non-RCTs found an association between physical training in HF patients and a small reduction of TNF-α and IL-6 concentrations, but not of CRP[8]. In the last 10 years, many RCTs have evaluated the effect of physical training on inflammation in patients with HF, but their results were divergent, which calls for an up-to-date systematic review.

To our knowledge, this is the first meta-analysis of RCTs that has evaluated the effects of physical training in HF patients regarding three different types of biomarkers: natriuretic peptides (BNP and NT-proBNP), cardiac troponins, and mediators of inflammation (CRP, TNF-α, and interleukins). Due to the diversity of physical training protocols (training modality, length of intervention, frequency, and intensity) and patient characteristics (age, ejection fraction, functional class, and cardiac resynchronization therapy), the current systematic review and meta-analysis conducted meta-regression analyses to examine the difference in biomarkers at follow-up between trained HF patients and controls and the potential predictors mentioned above.

METHODS

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) Statement for conduct and reporting [9].

Protocol and registration

This systematic review is registered in the International Prospective Register for Systematic Reviews (PROSPERO) (number CRD42020191215).

Eligibility criteria

RCTs of physical training in adults and older adults of both sexes diagnosed with HF were eligible for inclusion. Heart failure type (preserved, mid-range and reduced ejection fraction) was not considered as an inclusion or exclusion criteria. Exercise training included conventional training (aerobic training, resistance training, or a combination of the two). Cardiac rehabilitation was also included, although non-conventional modes of exercise training, such as yoga, tai chi, stretching, or physical therapy (e.g., functional electrical stimulation and inspiratory muscle training) were not. The comparator was usual care or an education control group, with no formally prescribed exercise training. Because some studies compared multiple exercise interventions with a single control group, we split this shared group into two groups with smaller sample sizes weighted in relation to the different exercise interventions. Thus, the number of analyses is greater than the number of included studies. This approach was applied to have reasonably independent comparisons and overcome a unit-of-analysis error that could contribute to multiple and correlated comparisons, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions*[10]. When trials reported more than one follow-up assessment, the shortest follow-up was used for data analysis. The duration of exercise training was not considered as an inclusion or exclusion criteria. Studies were eligible for inclusion if they reported one or more of the following outcomes in serum or plasma: BNP, NT-proBNP, cardiac troponins, CRP, TNF-α, IL-1ß, IL-6, IL-10 and IL-18. Only studies in English, Spanish, or Portuguese were included. We did not include conference abstracts.

Information sources and search

The article search included all the appropriate terms for “heart failure”, “exercise”, “natriuretic peptide, brain”, “CRP”, “inflammatory cytokines”, and “troponins” in the

selected databases. To amplify our search strategy, we did not use any terms referring to controls or study design. PubMed, Embase, CINAHL, SPORTDiscus and the Cochrane Library were searched using a combination of MeSH headings, keywords, and related entry terms to identify potentially relevant literature. The complete search strategy for the PubMed database is shown in Supplementary Box 1.

The search process was completed in May 2020. After combining the search results from different databases, the duplicates were removed. The records were managed using EndNote X7. A manual search (i.e. reference lists and citation searching) was also conducted of studies fulfilling the eligibility criteria.

Study selection and data collection process

Two authors (DMN and BN) independently screened the titles and abstracts of all studies found in the search to identify those that might meet the inclusion criteria. The reviewers were not blinded to the manuscripts' authors, institutions, or journals. Abstracts that did not provide sufficient information about the inclusion and exclusion criteria were retrieved for full-text evaluation. Full-text articles retained from the first stage were reassessed independently by the same two authors. Any disagreements were resolved by a third independent author (PMB).

Data items

A standardized, pre-piloted form (Microsoft® Excel® 2006) was used to extract data from the included studies for evidence synthesis. The following data were extracted from included studies: first author, publication year, title, objective, intervention type, study design, sample size, follow-up time, HF type, New York Heart Association (NYHA) functional classification and etiology, disease duration, clinical stability, and optimal pharmacological therapy, comorbidities, age, and evaluated outcomes. Post-intervention means ± standard deviations were extracted from continuous variables related to blood biomarker evaluation. Outcome data reported in graphics were extracted using WebPlotDigitizer 4.3 (Copyright 2010-2020 Ankit Rohatgi). Transformation methods were used for the small number of studies that showed results as confidence intervals (CIs), interquartile ranges, or standard error (SE)[11]. Relevant data were extracted from studies by two separate investigators (DMN and BN). Any disagreements were resolved by a third independent author (PMB). Corresponding authors were contacted as needed to obtain data not included in the published reports.

Risk of bias

A risk of bias assessment was performed for all included studies using the revised Cochrane risk of bias tool[12]. A standardized, pre-piloted form (Microsoft® Excel® 2006) was used to extract data from the included studies to assess study quality. Each study was evaluated based on the following items: bias arising from the randomization process, bias due to deviating from the intended intervention (the intention-to-treat effect), bias due to missing outcome data, bias measuring the outcome, and reporting bias. Each domain consisted of multiple questions and, using an algorithm with the answers, was classified as low risk, of some concern, or as a high risk of bias. The risk-of-bias assessment was performed by two independent reviewers (DMN and BN).

Summary measures, synthesis of results and sensitivity analysis

We provide a narrative synthesis of the findings from the included studies, structured around outcome type. The meta-analysis was conducted using RevMan software (Cochrane Review Manager, version 5.4), and univariate meta-regression was performed using R software (version 3.6.3). Blood biomarker outcomes are expressed as mean difference and 95% confidence interval (CI) between the intervention and control groups. We pooled the results using a random-effects meta-analysis. The physical training intervention group was compared with the non-intervention (control) group. *P*-values <0.05 were considered statistically significant.

The statistical heterogeneity of the treatment effect among studies was assessed using both the chi-squared test and the I^2 statistic. We considered I^2 values > 50% as indicative of substantial heterogeneity and a threshold *P*-value of 0.1 as statistically significant, in conformity with the *Cochrane Handbook for Systematic Reviews of Interventions*[10]. We explored the heterogeneity between studies using three strategies. First, we reran the meta-analyses by assessing the effect of individual studies on the overall results of the meta-analysis, removing one study at a time to determine whether a particular study could explain the heterogeneity. Second, we performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates of the intervention based on the following prespecified information: (1) intervention length (cut-off of 12 weeks); (2) weekly exercise frequency (cut-off of three sessions/week); (3) weekly amount of exercise (cut-off of 150 minutes/week); (4) exercise intensity (low, moderate or high); and (5) exercise modality (continuous aerobic, interval aerobic, or combined aerobic and resistance). Finally, univariate meta-regression models were

performed to assess clinical and methodological variables that could influence the association of exercise training with biomarkers levels. The variables were: (1) age, (2) sex, (3) left ventricular ejection fraction (LVEF), (4) NYHA functional classification (I and IV), (5) use of an implantable cardiac defibrillator or a cardiac resynchronization therapy device, and (6) exercise prescription (length of intervention, weekly exercise frequency, and weekly total exercise time). The univariate meta-regression was performed when there were at least 10 studies in a meta-analysis.

RESULTS

Study selection

The electronic search returned 2179 potentially relevant studies from the databases (PubMed=1460, Cochrane=550, CINAHL=70, Embase=52, and SPORTDiscus=47). Six studies were identified from a manual search of the reference lists of the selected studies. Following the removal of duplicates and ineligible studies, the titles and abstracts of 1562 studies were reviewed. The 54 full-text articles retained from this stage were reassessed, of which 33 trials (38 analyses) were included in the final meta-analysis. A detailed flowchart showing the study search and selection process is presented in Figure 1.

Study and participants characteristics

A general description of the included studies is provided in Table 1. Most of the 33 included studies were parallel RCTs. One study[13] was a crossover RCT. One study provided an analysis of two different age strata (≤ 55 and ≥ 65 years)[14], and four studies[15; 16; 17; 18] compared multiple exercise interventions with a control group, which was split in two control groups. Three trials[16; 18; 19] reported data in a graphical format. Two trials[20; 21] reported more than one follow-up assessment (12 and 24 weeks), and the shortest follow-up was used for data analysis. One trial[22] assessed NT-proBNP but did not report the results. This trial was not excluded because the other inflammation assessment data (CRP, TNF-α, IL-6) was shown. Some participants were overlapped in two studies[23; 24]; to avoid possible data duplication regarding BNP, this variable was extracted only from Passino et al.[24]. Cardiac troponin T results were reported by a single trial[25], although it was modeled as a dichotomous variable and stratified at the lower limit of detection. Hence, troponin T was not meta-analyzed. Since interleukins IL-10[26] and IL-18[22] were also reported by one trial, they were not meta-analyzed. None of the trials showed changes in troponin T, IL-10, or IL-18 concentrations after exercise training.

A total of 2310 randomized patients (1274 exercise training participants and 1036 controls) from eligible trials were included in this meta-analysis, with a mean age > 60 years in most studies. The trials included subjects of both sexes, except for three studies[27; 28; 29] that only included men. All patients met the diagnostic criteria for HF, but only three studies indicated that HF was classified as reduced ejection fraction (HFrEF)[14], preserved ejection fraction (HFpEF)[26] or both[30]. Ischemic heart disease and dilative cardiomyopathy were the most prevalent HF etiologies. Non-ischemic heart diseases, such as hypertension, atrial fibrillation, valve disease, Chagas disease and congenital heart disease, were also found in a few studies. Only five studies reported the duration of HF [14; 16; 28; 31; 32] (more than 6 months). Most of the studies included patients classified as NYHA II-III; seven studies[15; 23; 24; 32; 33; 34; 35] also included NYHA I patients, and three studies[20; 25; 36] included NYHA IV patients. Most studies included participants with a mean LVEF ≤ 40%. Only three studies[17; 26; 37] included participants with a mean LVEF > 40%. The most prevalent comorbidities were hypertension and diabetes mellitus, followed by dyslipidemia, arrhythmia, coronary artery disease or history of myocardial infarction, and smoking. Depression[30; 31], alcohol consumption[17], hypothyroidism[17] and chronic obstructive pulmonary disease [38] were also reported. Eight trials[14; 25; 28; 31; 35; 36; 38; 39] included patients receiving cardiac resynchronization therapy.

A detailed description of the interventions can be found in Table 1. Gademan et al.[40] compared the effects of periodic electrical somatosensory stimulation in patients with chronic HF with exercise training and usual care. Since this trial randomized the patients into three groups (electrical stimulation, exercise training and control), the data were extracted from the comparison between exercise training and control groups.

Most studies reported data on clinical stability or optimal pharmacological therapy prior to enrollment in the protocols, which ranged from four weeks to more than 12 months. Aerobic (continuous, interval, or both) training was the most common exercise intervention. Some studies[15; 19; 20; 26; 31; 32; 37; 40; 41] combined aerobic exercise (continuous or interval) with resistance training. One study[33] divided the same intervention group into continuous and interval aerobic training modalities. The intervention length varied from four weeks to 36 weeks. Only one trial[40] limited the intervention to two to three weeks. Exercise frequency ranged from two to seven sessions per week.

Of the 33 trials, 14 did not report data on adverse events. Only four studies[15; 26; 39; 42] reported minor adverse events related to exercise interventions, such as premature supraventricular and ventricular contractions, angina pectoris, severe hypotension,

palpitations, dyspnea, and musculoskeletal injury or discomfort. No major adverse events were reported. Dropout rates were less than 20% for most studies. Twelve studies did not report dropout data. Data on compliance or adherence was reported in 14 studies and was > 60% in 12 (Supplementary Table 1).

Risk of bias and publication bias assessment

All 38 analyses of the 33 included studies were assessed for methodological quality using the Cochrane Collaboration risk of bias tool (Supplementary Figure 1). A total of 89.5% were of some concern and 10.5% had a high risk of bias; none of the studies were rated as low risk. The concerns in most studies were related to reporting bias (94.7%), the randomization process (86.8%), and deviation from the intended intervention (50.0%). All studies had a low risk of bias regarding missing outcome data and most (97.4%) had low risk regarding outcome measurement.

Publication bias was evaluated with a funnel plot for BNP (Supplementary Figure 2A) and NT-proBNP (Supplementary Figure 2B), with the points for missing studies at the bottom of the plot. Since most of this area typically contains regions from small studies, publication bias is unlikely to be the underlying cause of this asymmetry. Given the limited number of studies included in the primary outcome meta-analysis, no further tests were run to distinguish between chance and real asymmetry.

Synthesis of results

BNP and NT-proBNP

According to pooled data from 11 studies (12 analyses, 247 exercise participants and 167 controls), exercise training was associated with decreased BNP (-62.2 pg/ml, 95% CI -116.8 to -7.6, p = 0.030; I^2 = 67%, p for heterogeneity < 0.01) (Figure 2A). According to data extracted from 14 studies (18 analyses, 810 exercise participants and 735 controls), exercise training was associated with decreased NT-proBNP (-182.4 pg/ml, 95% CI -298.2 to -66.5, p = 0.002; I^2 = 72%, p for heterogeneity < 0.01) (Figure 2B).

When heterogeneity was higher than 50%, studies were omitted individually from the meta-analyses to assess their influence on outcomes. Heterogeneity was reduced only in the BNP meta-analysis when three studies were removed[19,37,31] (I^2 = 45%. p = 0.070). Subgroup analysis demonstrated that an exercise frequency of more than three sessions per week was associated with a greater reduction in NT-proBNP levels (-514.9 pg/ml, 95% CI -756.0 to -273.9, p < 0.01; I^2 = 23%, p for heterogeneity = 0.270) (5 analyses, 80

exercise participants, and 71 controls). According to univariate meta-regression analysis, clinical and methodological variables had no influence on BNP levels after exercise training. In contrast, age was associated with a 12.1 pg/ml decrease in NT-proBNP level (95% CI -23.7 to -0.4, p = 0.041), especially in individuals > 77 years of age. Weekly exercise frequency was associated with a 392.1 pg/ml decrease in NT-proBNP level (95% CI -620.6 to -163.6, p < 0.01), and an exercise frequency > 3 sessions per week was responsible for more significant reductions.

Inflammation biomarkers

The results of eight studies (11 analyses, 651 exercise participants and 576 controls) showed that exercise training is associated with decreased CRP (-0.18 mg/dl, 95% CI -0.21 to -0.15, p < 0.01; I^2 = 0%, p for heterogeneity = 0.79) (Figure 3A).

A meta-analysis of seven studies (179 exercise participants and 142 controls) indicated that exercise training is associated with decreased TNF-α (-0.76 pg/ml, 95% CI -1.43 to -0.09, p = 0.030; I^2 = 56%, p for heterogeneity = 0.030) (Figure 3B). The exclusion of the only crossover clinical trial[13] reduced the heterogeneity for the TNF-α results (I^2 = 49%, p = 0.080). Subgroup analyses demonstrated that ≥ 150 minutes/week of exercise was associated with an even greater reduction in TNF-α levels (-2.51 pg/ml, 95% CI -3.67 to -1.35, p < 0.01; I^2 = 0%, p for heterogeneity = 0.860) (three analyses, 56 exercise participants and 56 controls).

A meta-analysis of three studies (93 exercise participants and 46 controls) demonstrated an association between exercise training and reduced IL-1ß (-0.24 pg/ml, 95% CI -0.38 to -0.09, p < 0.01; I^2 = 6%, p for heterogeneity = 0.350) (Figure 3C), and the results of eight studies (9 analyses, 202 exercise participants and 151 controls) demonstrated an association between exercise training and reduced IL-6 (-0.93 pg/ml, 95% CI -1.82 to -0.05, p = 0.040; I^2 = 59%, p for heterogeneity = 0.010) (Figure 3D). Subgroup analyses demonstrated that aerobic interval training was associated with lower IL-6 levels (-2.38 pg/ml, 95% CI -3.93 to -0.84, p = 0.040; I^2 = 21%, p for heterogeneity = 0.260) (two analyses, 54 exercise participants and 47 controls).

DISCUSSION

To the best of our knowledge, this systematic review represents the most comprehensive synthesis to date on the effects of physical training on different biomarkers with respect to the multifaceted pathogenesis of HF. According to pooled data

from 33 studies, physical training was associated with lower natriuretic peptides (BNP and NT-proBNP) and biomarkers of inflammation (CRP, TNF-α, IL-1ß, and IL-6).

Our data are in accordance with another systematic review[7] in which peptides, BNP, and NT-proBNP, were reduced after conventional exercise training in HF patients, although these reviews included studies with other designs in addition to RCTs[7]. In addition, we did not exclude trials with HFpEF patients. For this reason, we conducted a meta-regression using mean ejection fraction, as well as subgroup analyses, excluding studies with NYHA IV patients, showing that HF severity according to left ventricular function and functional class did not interfere with the BNP and NT-proBNP results. Instead, univariate meta-regression analysis showed that older age had a greater effect size on NT-proBNP reduction and that age was responsible for 13% of the heterogeneity in the results of this biomarker.

The subgroup analysis demonstrated that an exercise frequency of more than three sessions per week leads to a greater effect size on NT-proBNP results, which could be associated with greater energy expenditure. The meta-regression analysis also demonstrated that exercise frequency was responsible for 55% of the heterogeneity, and that at least three training sessions per week is associated with a greater decrease in NT-proBNP. Smart et al[43], in an individual patient meta-analysis, demonstrated that a mean weekly energy expenditure of 457 kcal was sufficient for significant changes in BNP, but not NT-proBNP. However, the authors did find an association between natriuretic peptide level and weekly training frequency.

Natriuretic peptides have been increasingly used as a diagnostic/prognostic tool and a therapeutic target for patients with HF. Findings from RCTs on HF patients suggest that physical training could improve functional capacity (VE/VCO_2 slope and peak VO_2) and left ventricular compliance and could reduce levels of cardiac stress biomarkers (BNP and NT-proBNP)[35; 21; 23].

Unlike the results of our review, Smart et al.[6] found that exercise reduced plasma TNF-α concentrations in only four of 11 included studies, including one study that assessed TNF-α response through functional electrical stimulation. Their plasma IL-6 results were even more limited. Although we found that aerobic interval training was associated with lower levels of IL-6, only one study in their review indicated that exercise had a positive effect on this biomarker, and IL-1ß and IL-10 did not change in response to physical training. The methodological and clinical heterogeneity of the studies prevented these authors from performing a meta-analysis of the data. In a previous

systematic review and meta-analysis (RCTs and non-RCTs), Pearson et al.[8] found that physical training had a minimally favorable effect on circulating TNF-α and IL-6 levels in HF patients and had no effect on CRP. Clearly, however, the present systematic review showed lower clinical and statistical heterogeneity among studies, as well as meta-regression analyses, which helped explain the remaining heterogeneity.

Our findings indicate that physical training reduced TNF-α and that the frequency further modified the reduction: subgroup analyses showed that weekly training ≥ 150 minutes of exercise led to the greatest reduction. Smart et al.[6] found no relationship between the amount or frequency of physical training and TNF-α changes, but they considered fewer studies, included observational studies, and did not perform a meta-regression.

This systematic review and meta-analyses has some limitations, principally in not considering HF etiology, medication use, and other comorbidities, such as hypertension and diabetes. In addition, biomarker concentrations could have been affected by methods used for collection and sample preparation, the time since the last exercise session, and whether plasma or serum measurements were performed. Several other biomarkers have already been associated with HF, and strategies that combine multiple markers could someday help guide the therapeutic approach. Moreover, we could not analyze the effects of physical training on cardiac troponins and other cytokines, such as IL-10 and IL-18, because no RCTs involving these biomarkers could be found.

CONCLUSION

This meta-analysis updates the findings from previous systematic reviews and provides strong evidence about the positive effects of exercise training on myocardial stress reduction and inflammatory response modulation in HF. Furthermore, we highlight aspects of exercise prescription that can guide training for patients with HF, i.e., that older age and at least three sessions per week are associated with a greater decrease in NT-proBNP. In addition, at least 150 minutes of weekly training is necessary to reduce TNF-α, and aerobic interval training seems to be the most suitable modality for reducing IL-6.

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Conflicts of Interest: None declared.

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Figure legends:

Figure 1. PRISMA flowchart outlining the literature search process.

Figure 2. (A) Absolute changes in B-type natriuretic peptide (BNP) on physical training. (B) Absolute changes in N-terminal pro-B-type natriuretic peptide (NT-proBNP) on physical training.

Figure 3. (A) Absolute changes in C-reactive protein (CRP). (B) Absolute changes in tumor necrosis factor α (TNF-α) on physical training. (C) Absolute changes in interleukin (IL) 1ß on physical training. (D) Absolute changes in interleukin (IL) IL-6 on physical training.

Supplementary Information:

Box 1. Search strategy used in the database searches.

Supplementary Figure 1. Cochrane risk-of-bias tool for randomized trials (RoB 2.0).

Supplementary Figure 2. (A) Funnel plot for B-type natriuretic peptide (BNP). (B) Funnel plot for N-terminal pro-B-type natriuretic peptide (NT-proBNP).

Supplementary Table 1. Data on compliance or adherence reported in the studies.

Table 1 Studies included in the review and detailed exercise intervention characteristics

Study	Control participant characteristics	Active participant characteristics	Control Group Intervention	Modality of exercise intervention	Duration	Sessions/ week	Total time/ session	Intensity
Abolahrari-Shirazi et al, 2018[a]	57.3±9.4 y, LVEF 35.0±5.5%, NYHA I-III	56.8±8.7 y, LVEF 34.4±5.3% NYHA I-III	Usual care	Combined training (30 min aerobic plus 15 min RT)	7 weeks	3	45 min	Aerobic: 40-70% VO_{2peak} Resistance: 40-60% 1RM; 2 sets of 10 rep., 4 exercises
Abolahrari-Shirazi et al, 2018[b]	57.3±9.4 y, LVEF 35.0±5.5%, NYHA I-III	57.6±7.8 y, LVEF 33.8±6.1% NYHA I-III	Usual care	Aerobic (20 min cycling, 10 min on arm ergometer, and 15 min on treadmill)	7 weeks	3	45 min	40-70% VO_{2peak}
Adamopoulos et al, 2002	55.0±9.8 y, LVEF 23.2±6.4%, NYHA II-III	55.0±9.8 y, LVEF 23.2±6.4%, NYHA II-III	Usual care	Aerobic (home-based, cycling, 50 rpm)	12 weeks	5	30 min	60-80% max HR
Ahmad et al, 2014 (Biomarker Substudy HF ACTION Trial)	59.0±12.8 y, LVEF 24.7±7.8 /% NYHA II–IV	59.0±12.3 y, LVEF 24.5±7.4% NYHA II–IV	Usual care	Aerobic (walking, treadmill or cycling)	12 weeks	3	15-30 min	60% HRR and ramped up
Aksoy et al, 2015[a]	57.5±11.2 y, LVEF 51.7±6.2% NYHA II–III	63.7±8.8 y, LVEF 50.3±6.9% NYHA II–III	Sedentary Lifestyle	Intermittent aerobic training (cycling)	10 weeks	3	35 min (included 5 min WU and CD, each)	50-75% VO_{2peak}; total of 17 cycles of low (30 sec) and high intensity (60 sec) bouts in a session.
Aksoy et al, 2015[b]	57.5±11.2 y, LVEF 51.7±6.2% NYHA II–III	59.6±6.9 y, LVEF 52±4.9% NYHA II–III	Sedentary lifestyle	Continuous aerobic training (cycling)	10 weeks	3	35 min (included 5 min WU and CD, each)	50-75% VO_{2peak}
Butterfield et al, 2008	75.0±12.0 y, LVEF 35±14% NYHA II–III	66.0±10.0 y, LVEF 34±11% NYHA II–III	Usual care, exercise, diet, and medication therapy education	Combined training (1 session/week at hospital - circuit training, and daily home-based walking - 45-60 min)	12 weeks	7	> 45 min (included 10 min WU and CD, each)	Not reported
Butts et al, 2018	58.2±12.8 y, LVEF 35.5±12.7% NYHA II–III	60.0±8.7 y, LVEF 32.8±15.9% NYHA II–III	Attention control	Aerobic (walking)	12 weeks	3	30-45 min	60-70% max HR

Byrkjeland et al, 2011	71.5±7.8 y, LVEF 30.8±9.4% NYHA II–III	68.8±7.9 y, LVEF 30.2±7.6% NYHA II–III	Usual care	Aerobic (interval training and group-based counseling – 15-30 min)	16 weeks	2	50 min (included WU and CD periods)	3 high intensity intervals (15-18 Borg scale; 90-95% max HR) and 2 of moderate (11-13 Borg scale; 50-60% max HR)
Conraads et al, 2007	61.0±4.0 y, LVEF 28±5% NYHA >III	57.0±2.0 y, LVEF 27±5% NYHA >III	Usual care	Aerobic (cycling and waking)	16 weeks	3	60 min (included 5 min WU and CD, each)	90% HR at VT
De Meirelles et al, 2014	55.0±2.0 y, LVEF 31.7±2% NYHA II-III	54.0±3.0 y, LVEF 31.2±1.6% NYHA II-III	Usual care	Combined training (30 min treadmill and RT)	24 weeks	3	90 min	Aerobic: HR 5-15% above VT. Resistance: 2 to 3 sets of 10-15 rep., 8-10 exercises
Eleuteri et al, 2013	63.0±6.3 y, LVEF 30.0±5.7% NYHA II-III	66.0±7.0 y, LVEF 28.0±7.0% NYHA II-III	Instruction to continue normal lifestyle activities	Aerobic (home-based, cycling)	12 weeks	5	40 min (included 5 min WU and CD, each)	Power and HR at VAT
Erbs et al, 2010	62.0±10.0 y, LVEF 25.0±4.0% NYHA IIIb	60.0±11.0 y, LVEF 24.0±5.0% NYHA IIIb	Sedentary lifestyle	Aerobic (home-based, cycling)	12 weeks	5	20-30 min	HR at 60% VO_{2max}
Fernandez-Silva et al, 2017	48.0±7.0 y, LVEF 29.3±6.6% NYHA I–III	51.0±7.0 y, LVEF 29.6±6.1% NYHA I–III	Not reported	Aerobic (cycling: interval or continuous training)	12 weeks	3	40 min	Interval: 1 min at RCP HR and 2 min at ANT HR. Continuous: HR = [RCP HR + 2x (ANT HR)]
Fu et al, 2013[a]	67.8±9.7 y, LVEF 38.0±14.7% NYHA II–III	66.3±8.1 y, LVEF 38.6±18.6% NYHA II–III	General healthcare	Aerobic interval training (cycling)	12 weeks	3	30 min (included 3 min WU and CD, each)	Five 3-minute intervals at 80% VO_{2peak}, separated by 3-minute exercise at 40% VO_{2peak}
Fu et al, 2013[b]	67.8±9.7 y, LVEF 38.0±14.7% NYHA II–III	66.3±8.1 y, LVEF 38.6±18.6% NYHA II–III	General healthcare	Moderate continuous training (cycling)	12 weeks	3	30 min (included 3 min WU and CD, each)	60% VO_{2peak}
Gademan et al, 2013	64.0±9.0 y,	60.0±12.0 y,	Usual care	Combined training (30 min	4-6 sessions	2-3	75 min	Aerobic: HR at VT

	LVEF 32.0±7.0% NYHA II–III	LVEF 32.0±8.0% NYHA II–III		cycling and 15 min rowing or walking, and RT)				Resistance: 1 set; 25 rep.; 40% 1RM
Gary et al, 2011	61.0±10.0 y, LVEF 27.0±9.0% NYHA II–III	59.0±11.0 y, LVEF 23.0±8.0% NYHA II–III	Performed light stretching and flexibility exercises	Combined training (walking and RT)	12 weeks	3 (AT) 2 (RT)	30-60 min 60-90 min (included 5 min WU)	Aerobic: 50-70% HRR (6MWT) and 12-15 Borg scale. Resistance: 2-3 sets; 12-15 rep.; progressive elastic bands
Guazzi et al, 2012	Total sample: 67.8±5.9 years, LVEF 36.5±4.9% NYHA II–III	Total sample: 67.8±5.9 years, LVEF 36.5±4.9% NYHA II–III	Not reported	Aerobic (cycling)	24 weeks	4	40 min	60-80% HRR
Jonsdottir et al, 2006	69.0±5.3 y, LVEF 40.6±13.7% NYHA II–III	68.0±6.6 y, LVEF 41.5±13.6% NYHA II–III	Continuing previous physical activity	Combined training (15 min cycling and 20 min circuit RT)	20 weeks	2	40 min (included 5 min WU)	Aerobic: 50% of peak workload, then increased. Resistance: 20-25% 1RM, increased to 35-40% 1RM
Kobayashi et al, 2003	62±2 y, LVEF 33±2% NYHA II-III	55±2 y, LVEF 29±2% NYHA II-III	Sedentary lifestyle	Aerobic (2 sets of 15 min/day on cycling)	12 weeks	2-3	2 sets of 15 min/day	HR at VT or 13-20 Borg scale
Lima et al, 2010	50.0±6.6 y, LVEF 37.0±7.6% NYHA I-III	48.9±8.8 y, LVEF 35.7±8.1% NYHA I-III	Inactive control group	Aerobic (walking)	12 weeks	3	60 min (included 15 min of WU and CD, each)	55-65% peak HR
Linke et al, 2005	52.0±3.0 y, LVEF 27.0±3.0% NYHA II-III	55.0±2.0 y, LVEF 26.0±3.0% NYHA II-III	Sedentary lifestyle	Aerobic (home-based, ciclyng)	24 weeks	5	20 min	HR at 70% VO_{2max}
Malfatto et al, 2009	67.0±9.0 y, LVEF 33.0±6.0% NYHA I-III	65.0±11.0 y, LVEF 31.0±6.0% NYHA I-III	Untrained control group	Cardiac rehabilitation (40 min cycling or treadmill)	12 weeks	3	60 min (included 15-20 min of WU)	Initial target HR at 60% VO_{2peak}
Meyer et al, 2004	54.0±9.0 y, LVEF 30.0±11.0% NYHA II-III	58.0±10.0 y, LVEF 29.0±13.0% NYHA II-III	Not reported	Aerobic (cycling)	12 weeks	4	45 min	HR at ANT
Nilsson et al, 2010	71.5±7.9 years, LVEF 30.9±9.6% NYHA II-III	68.9±7.9 years, LVEF 29.9±7.6% NYHA II-III	Usual care	Aerobic (interval training)	16 weeks	2	50 min	3 intervals of high intensity (15-18 Borg scale; 90-95%, max HR) and 2 of moderate (11-13

								Borg scale; 50-60% max HR)
Norman et al, 2012	63±15.2 y, LVEF 32.3±5.4% NYHA II-IV	56±12.1 y, LVEF 34±6.3% NYHA II-IV	Educational sessions (HF symptoms medications, sodium and fluid restrictions	Combined training (aerobic and RT)	12 weeks	3 (AT) 2 (RT)	60 min (included 15 min of WU and CD, each)	Aerobic: 40-60% HRR or 11-14 Borg scale. Resistance: 1 set; 10-15 rep.
Parrinello et al, 2009	63.2±5.0 y, LVEF 38.9±3.9% NYHA II-III	62.3±4.9 y, LVEF 39.0±3.5% NYHA II-III	Medical therapy and dietary recommendations with restricted fluid intake	Aerobic (walking)	10 weeks	5	30 min	Mild to moderate intensity
Passino et al, 2006	60.0±12.8 y, LVEF 32.3±14.1% NYHA I-III	61.0±13.27 y, LVEF 35.3±10.6% NYHA I-III	Usual lifestyle	Aerobic (home-based, cycling)	36 weeks	3	30 min	HR at 65% VO_{2peak}
Passino et al, 2008	63.0±8.7 y, LVEF 35.9±11.3% NYHA I-III	61±16.8 y, LVEF 35.1±8.4% NYHA II-III	Usual lifestyle	Aerobic (home-based, ciclyng)	36 weeks	3	30 min	HR at 65% VO_{2peak}
Sandri et al, 2012[a] (LEICA Study)	49.0±19.4 y, LVEF 28.0±19.5% NYHA II-III	50.0±19.4 y, LVEF 27.0±23.2% NYHA II-III	Usual care	Aerobic (cycling)	4 weeks	4	20 min	70% symptom limited VO_{2peak}
Sandri et al, 2012[b] (LEICA Study)	72.0±11.7 y, LVEF 28±23.2% NYHA II-III	72.0±15.5 y, LVEF 29±23.2% NYHA II-III	Usual care	Aerobic (cycling)	4 weeks	4	20 min	70% symptom limited VO_{2peak}
Sarullo et al, 2006	52.9±4.9 y, LVEF 28.9±4.0% NYHA II-III	53.1±6.1 y, LVEF 29.2±5.0% NYHA II-III	To continue previous physical activity	Aerobic (cycling)	12 weeks	3	30 min	60-70% VO_{2peak}
Stevens et al, 2015	64.4±6.3 y, LVEF 35.0±2.0% NYHA I-III	66.6±3.1 y, LVEF 39.0±3.0% NYHA I-III	Usual care	Combined training (2 cycling bouts followed by 2 bouts of walking on a treadmill, and RT)	12 weeks	5x fortnight	>30 min	Aerobic: HR at 2nd VT and 14-16 Borg scale. Resistance: 2-3 sets; 10-15 rep.; 50-70% 1RM
Trippel et al, 2017 (Ex-DHF pilot study post hoc analysis)	65.0±6.0 y, LVEF 67.0±7.0% NYHA II-III	64.0±8.0 y, LVEF 68.0±7.0% NYHA II-III	Usual care	Combined training (20-40 min cycling and RT)	12 weeks	2-3 (AT) 2 (RT)	>20 min	Aerobic: 50-60% to 70% VO_{2peak}. Resistance: 1 set; 15 rep.; 60-65% 1RM

Van Dissel et al, 2009	40.0±15.4 y, LVEF 26.0±8.0% NYHA II-III	39.9±8.6 y, LVEF 28.0±7.0% NYHA II-III	Usual care	Aerobic (home-based exercise training)	24 weeks	3	45 min	80% HRR
Wisløff et al, 2007[a]	75.5±13.0 y, LVEF 26.2±8.0%	74.4±12.0 y, LVEF 32.8±4.8%	Standard advice regarding physical activity and 47 min of treadmill walking at 70% HR peak every 3 weeks	Moderate continuous training (treadmill walking)	12 weeks	3	47 min	70-75% peak HR
Wisløff et al, 2007[b]	75.5±13.0 y, LVEF 26.2±8.0%	76.5±9.0 y, LVEF 28.0±7.3%	Standard advice regarding physical activity and 47 min of treadmill walking at 70% HR peak every 3 weeks	Aerobic interval training (treadmill walking)	12 weeks	3	38 min	Four 4-minute intervals at 90-95% HR peak separated by 3-minute active pauses, walking at 50-70% HR peak

Data expressed as mean ± SD. ANT: Anaerobic threshold; AT: Aerobic training; CD: Cool-down; HR: Heart rate; HRR: Heart rate reserve; LVEF: Left ventricle ejection fraction; RCP: Respiratory compensation point; RM: Repetition maximum; RT: Resistance training; VAT: Ventilatory anaerobic threshold; VT: Ventilatory threshold; WU: Warm-up; Y: Years. [a, b] indicating two different analysis from the same study.

Figure 1

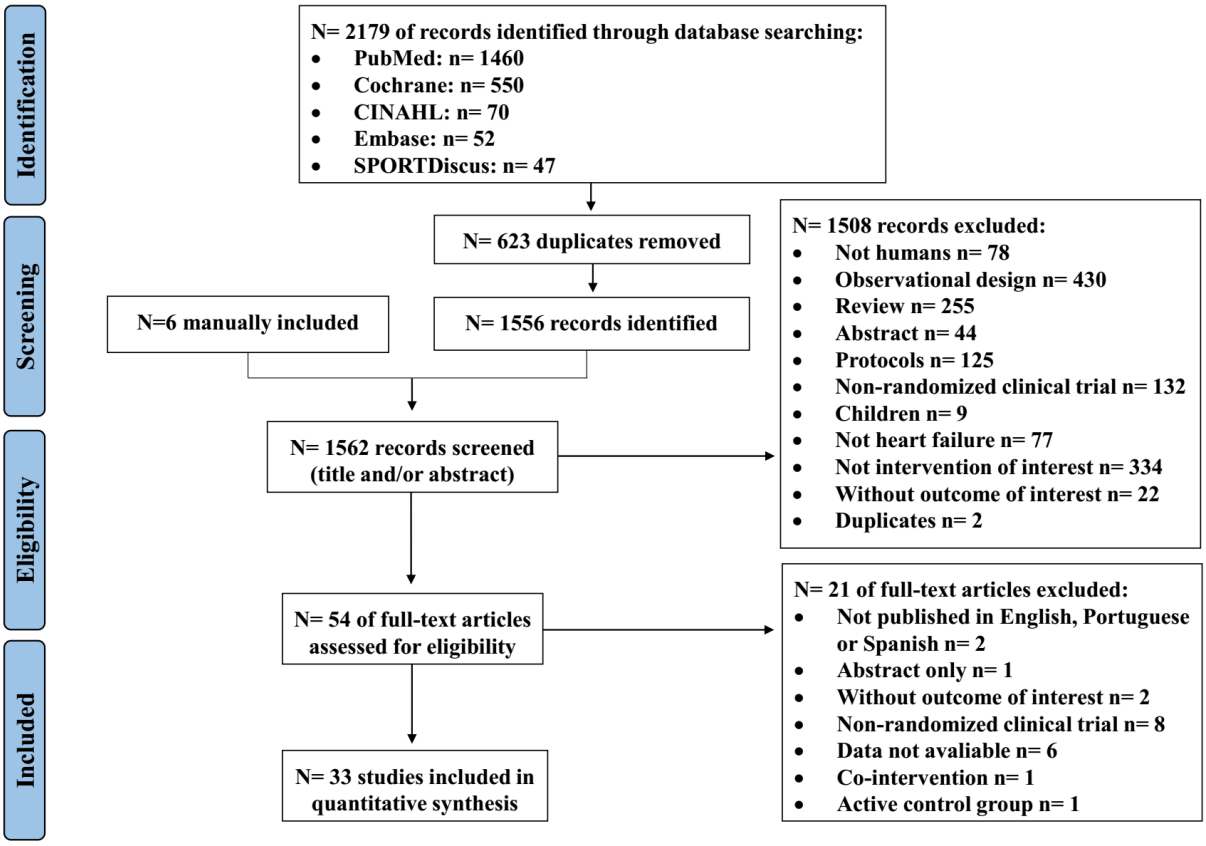
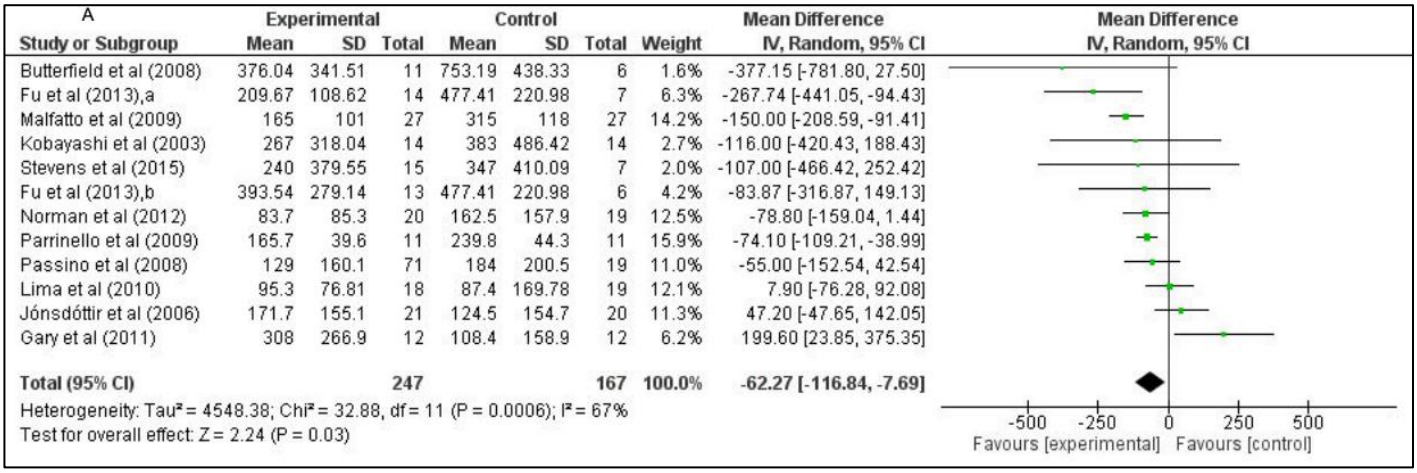

Identification
Screening
Eligibility
Included
N= 2179 of records identified through database searching:
PubMed: n= 1460
Cochrane: n= 550
CINAHL: n= 70
Embase: n= 52
SPORTDiscus: n= 47
N= 623 duplicates removed
N=6 manually included
N= 1556 records identified
N= 1562 records screened (title and/or abstract)
N= 1508 records excluded:
Not humans n= 78
Observational design n= 430
Review n= 255
Abstract n= 44
Protocols n= 125
Non-randomized clinical trial n= 132
Children n= 9
Not heart failure n= 77
Not intervention of interest n= 334
Without outcome of interest n= 22
Duplicates n= 2
N= 54 of full-text articles assessed for eligibility
N= 21 of full-text articles excluded:
Not published in English, Portuguese or Spanish n= 2
Abstract only n= 1
Without outcome of interest n= 2
Non-randomized clinical trial n= 8
Data not avaliable n= 6
Co-intervention n= 1
Active control group n= 1
N= 33 studies included in quantitative synthesis

Figure 2


A
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Butterfield et al (2008) 376.04 341.51 11 753.19 438.33 6 1.6% -377.15 [-781.80, 27.50]
Fu et al (2013),a 209.67 108.62 14 477.41 220.98 7 6.3% -267.74 [-441.05, -94.43]
Malfatto et al (2009) 165 101 27 315 118 27 14.2% -150.00 [-208.59, -91.41]
Kobayashi et al (2003) 267 318.04 14 383 486.42 14 2.7% -116.00 [-420.43, 188.43]
Stevens et al (2015) 240 379.55 15 347 410.09 7 2.0% -107.00 [-466.42, 252.42]
Fu et al (2013),b 393.54 279.14 13 477.41 220.98 6 4.2% -83.87 [-316.87, 149.13]
Norman et al (2012) 83.7 85.3 20 162.5 157.9 19 12.5% -78.80 [-159.04, 1.44]
Parrinello et al (2009) 165.7 39.6 11 239.8 44.3 11 15.9% -74.10 [-109.21, -38.99]
Passino et al (2008) 129 160.1 71 184 200.5 19 11.0% -55.00 [-152.54, 42.54]
Lima et al (2010) 95.3 76.81 18 87.4 169.78 19 12.1% 7.90 [-76.28, 92.08]
Jónsdóttir et al (2006) 171.7 155.1 21 124.5 154.7 20 11.3% 47.20 [-47.65, 142.05]
Gary et al (2011) 308 266.9 12 108.4 158.9 12 6.2% 199.60 [23.85, 375.35]
Total (95% CI) 247 167 100.0% -62.27 [-116.84, -7.69]
Heterogeneity: Tau² = 4548.38; Chi² = 32.88, df = 11 (P = 0.0006); I² = 67%
Test for overall effect: Z = 2.24 (P = 0.03)
-500 -250 0 250 500
Favours [experimental] Favours [control]

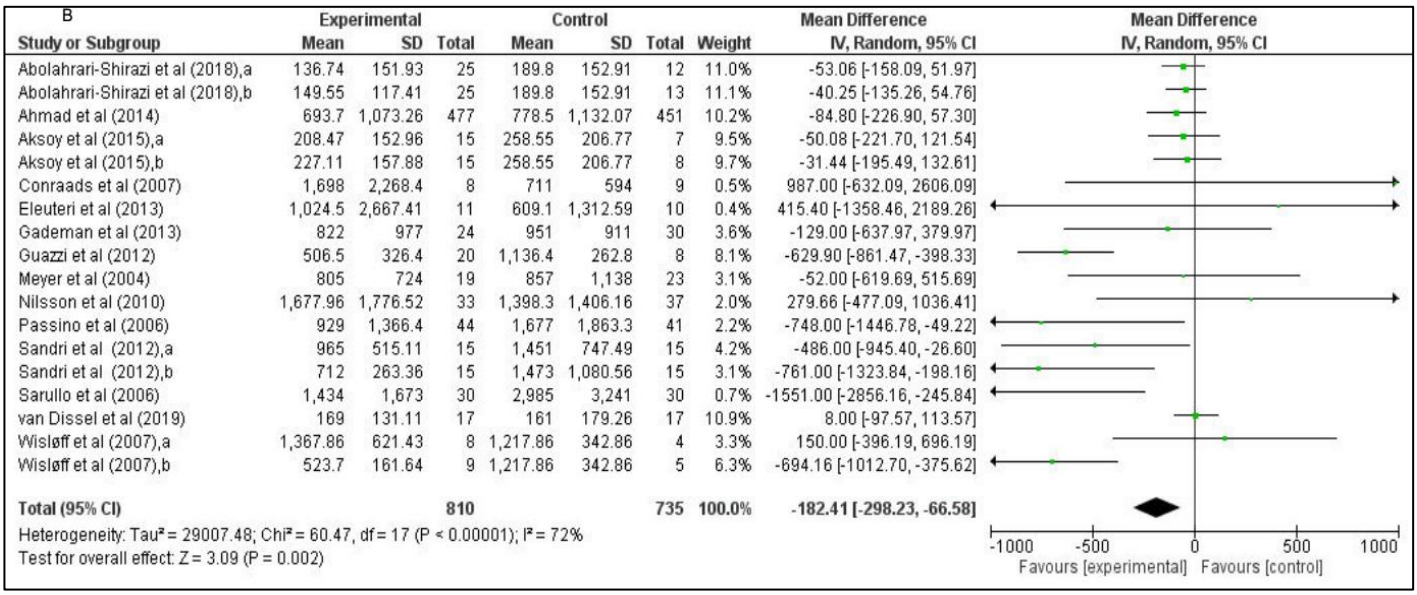
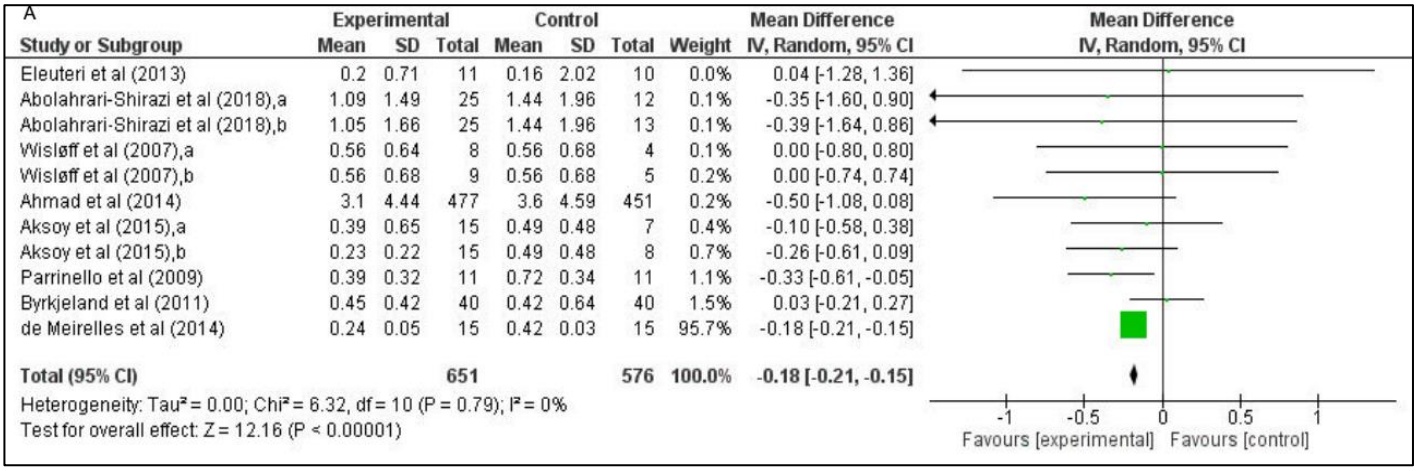
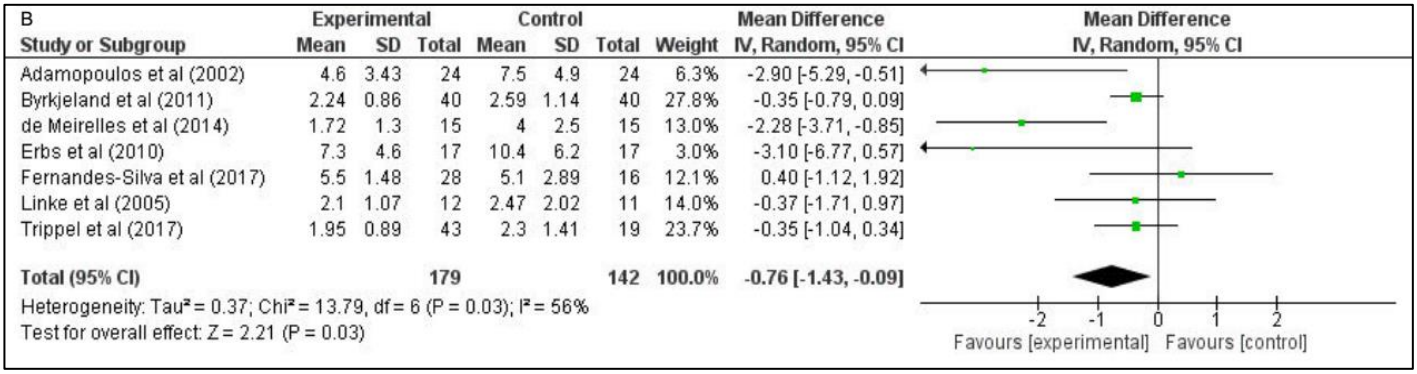
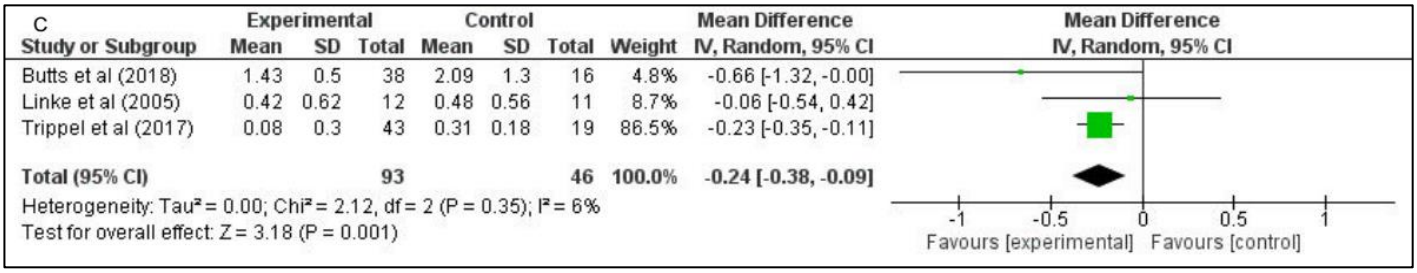
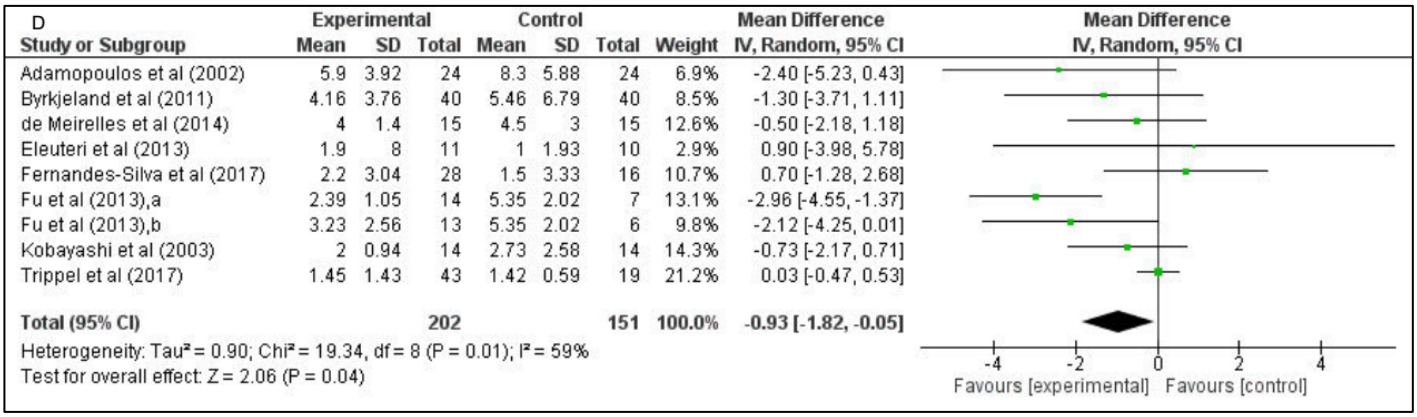

B
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Abolahrari-Shirazi et al (2018),a 136.74 151.93 25 189.8 152.91 12 11.0% -53.06 [-158.09, 51.97]
Abolahrari-Shirazi et al (2018),b 149.55 117.41 25 189.8 152.91 13 11.1% -40.25 [-135.26, 54.76]
Ahmad et al (2014) 693.7 1,073.26 477 778.5 1,132.07 451 10.2% -84.80 [-226.90, 57.30]
Aksoy et al (2015),a 208.47 152.96 15 258.55 206.77 7 9.5% -50.08 [-221.70, 121.54]
Aksoy et al (2015),b 227.11 157.88 15 258.55 206.77 8 9.7% -31.44 [-195.49, 132.61]
Conraads et al (2007) 1,698 2,268.4 8 711 594 9 0.5% 987.00 [-632.09, 2606.09]
Eleuteri et al (2013) 1,024.5 2,667.41 11 609.1 1,312.59 10 0.4% 415.40 [-1358.46, 2189.26]
Gademan et al (2013) 822 977 24 951 911 30 3.6% -129.00 [-637.97, 379.97]
Guazzi et al (2012) 506.5 326.4 20 1,136.4 262.8 8 8.1% -629.90 [-861.47, -398.33]
Meyer et al (2004) 805 724 19 857 1,138 23 3.1% -52.00 [-619.69, 515.69]
Nilsson et al (2010) 1,677.96 1,776.52 33 1,398.3 1,406.16 37 2.0% 279.66 [-477.09, 1036.41]
Passino et al (2006) 929 1,366.4 44 1,677 1,863.3 41 2.2% -748.00 [-1446.78, -49.22]
Sandri et al (2012),a 965 515.11 15 1,451 747.49 15 4.2% -486.00 [-945.40, -26.60]
Sandri et al (2012),b 712 263.36 15 1,473 1,080.56 15 3.1% -761.00 [-1323.84, -198.16]
Sarullo et al (2006) 1,434 1,673 30 2,985 3,241 30 0.7% -1551.00 [-2856.16, -245.84]
van Dissel et al (2019) 169 131.11 17 161 179.26 17 10.9% 8.00 [-97.57, 113.57]
Wisløff et al (2007),a 1,367.86 621.43 8 1,217.86 342.86 4 3.3% 150.00 [-396.19, 696.19]
Wisløff et al (2007),b 523.7 161.64 9 1,217.86 342.86 5 6.3% -694.16 [-1012.70, -375.62]
Total (95% CI) 810 735 100.0% -182.41 [-298.23, -66.58]
Heterogeneity: Tau² = 29007.48; Chi² = 60.47, df = 17 (P < 0.00001); I² = 72%
Test for overall effect: Z = 3.09 (P = 0.002)
-1000 -500 0 500 1000
Favours [experimental] Favours [control]

Figure 3


A
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Eleuteri et al (2013) 0.2 0.71 11 0.16 2.02 10 0.0% 0.04 [-1.28, 1.36]
Abolahrari-Shirazi et al (2018),a 1.09 1.49 25 1.44 1.96 12 0.1% -0.35 [-1.60, 0.90]
Abolahrari-Shirazi et al (2018),b 1.05 1.66 25 1.44 1.96 13 0.1% -0.39 [-1.64, 0.86]
Wisløff et al (2007),a 0.56 0.64 8 0.56 0.68 4 0.1% 0.00 [-0.80, 0.80]
Wisløff et al (2007),b 0.56 0.68 9 0.56 0.68 5 0.2% 0.00 [-0.74, 0.74]
Ahmad et al (2014) 3.1 4.44 477 3.6 4.59 451 0.2% -0.50 [-1.08, 0.08]
Aksoy et al (2015),a 0.39 0.65 15 0.49 0.48 7 0.4% -0.10 [-0.58, 0.38]
Aksoy et al (2015),b 0.23 0.22 15 0.49 0.48 8 0.7% -0.26 [-0.61, 0.09]
Parrinello et al (2009) 0.39 0.32 11 0.72 0.34 11 1.1% -0.33 [-0.61, -0.05]
Byrkjeland et al (2011) 0.45 0.42 40 0.42 0.64 40 1.5% 0.03 [-0.21, 0.27]
de Meirelles et al (2014) 0.24 0.05 15 0.42 0.03 15 95.7% -0.18 [-0.21, -0.15]
Total (95% CI) 651 576 100.0% -0.18 [-0.21, -0.15]
Heterogeneity: Tau² = 0.00; Chi² = 6.32, df = 10 (P = 0.79); I² = 0%
Test for overall effect: Z = 12.16 (P < 0.00001)
-1 -0.5 0 0.5 1
Favours [experimental] Favours [control]


B
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Adamopoulos et al (2002) 4.6 3.43 24 7.5 4.9 24 6.3% -2.90 [-5.29, -0.51]
Byrkjeland et al (2011) 2.24 0.86 40 2.59 1.14 40 27.8% -0.35 [-0.79, 0.09]
de Meirelles et al (2014) 1.72 1.3 15 4 2.5 15 13.0% -2.28 [-3.71, -0.85]
Erbs et al (2010) 7.3 4.6 17 10.4 6.2 17 3.0% -3.10 [-6.77, 0.57]
Fernandes-Silva et al (2017) 5.5 1.48 28 5.1 2.89 16 12.1% 0.40 [-1.12, 1.92]
Linke et al (2005) 2.1 1.07 12 2.47 2.02 11 14.0% -0.37 [-1.71, 0.97]
Trippel et al (2017) 1.95 0.89 43 2.3 1.41 19 23.7% -0.35 [-1.04, 0.34]
Total (95% CI) 179 142 100.0% -0.76 [-1.43, -0.09]
Heterogeneity: Tau² = 0.37; Chi² = 13.79, df = 6 (P = 0.03); I² = 56%
Test for overall effect: Z = 2.21 (P = 0.03)
-2 -1 0 1 2
Favours [experimental] Favours [control]

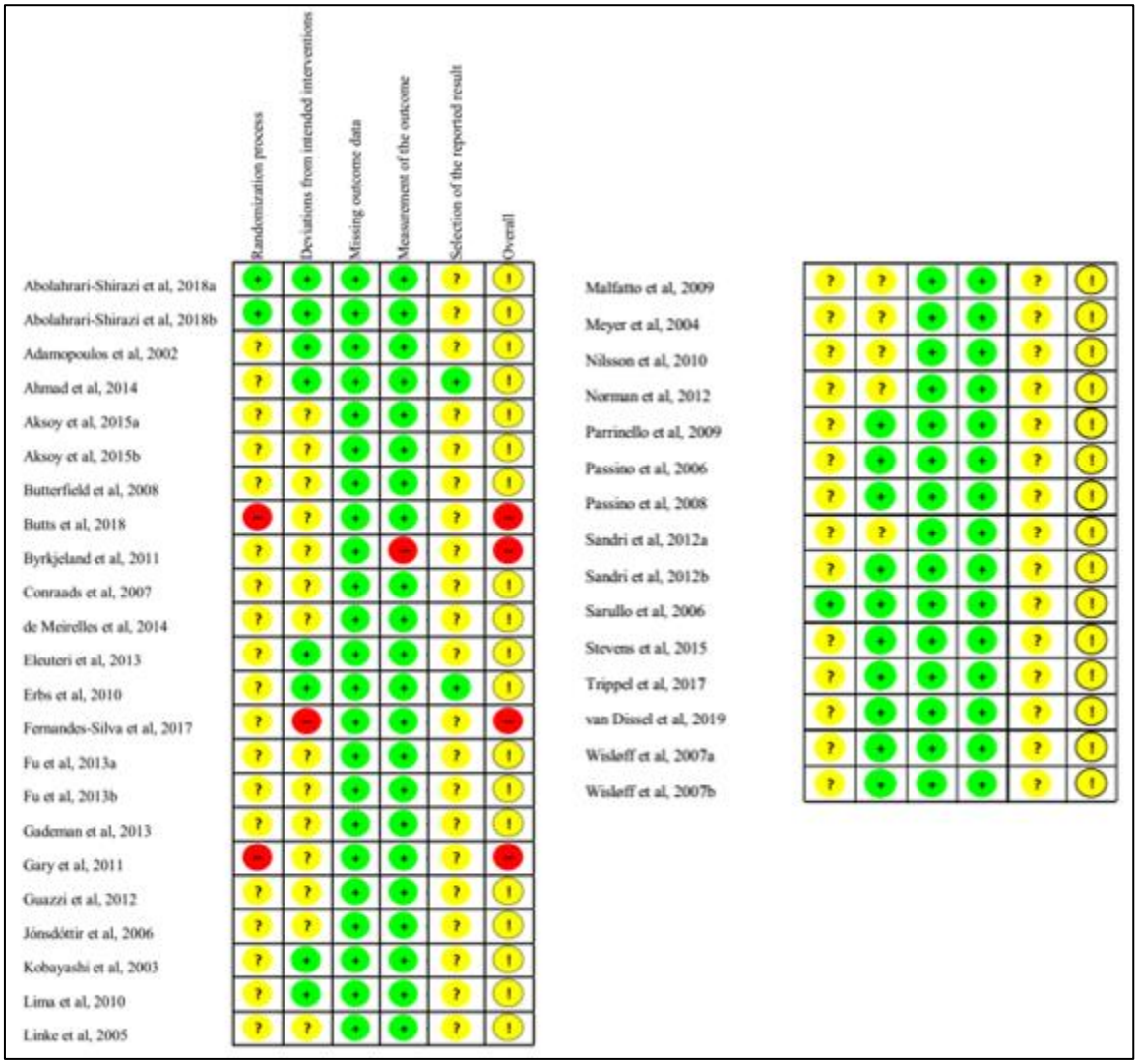

C
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Butts et al (2018) 1.43 0.5 38 2.09 1.3 16 4.8% -0.66 [-1.32, -0.00]
Linke et al (2005) 0.42 0.62 12 0.48 0.56 11 8.7% -0.06 [-0.54, 0.42]
Trippel et al (2017) 0.08 0.3 43 0.31 0.18 19 86.5% -0.23 [-0.35, -0.11]
Total (95% CI) 93 46 100.0% -0.24 [-0.38, -0.09]
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 2 (P = 0.35); I² = 6%
Test for overall effect: Z = 3.18 (P = 0.001)
-1 -0.5 0 0.5 1
Favours [experimental] Favours [control]


D
Experimental
Control
Mean Difference
Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI
IV, Random, 95% CI
Adamopoulos et al (2002) 5.9 3.92 24 8.3 5.88 24 6.9% -2.40 [-5.23, 0.43]
Byrkjeland et al (2011) 4.16 3.76 40 5.46 6.79 40 8.5% -1.30 [-3.71, 1.11]
de Meirelles et al (2014) 4 1.4 15 4.5 3 15 12.6% -0.50 [-2.18, 1.18]
Eleuteri et al (2013) 1.9 8 11 1 1.93 10 2.9% 0.90 [-3.98, 5.78]
Fernandes-Silva et al (2017) 2.2 3.04 28 1.5 3.33 16 10.7% 0.70 [-1.28, 2.68]
Fu et al (2013),a 2.39 1.05 14 5.35 2.02 7 13.1% -2.96 [-4.55, -1.37]
Fu et al (2013),b 3.23 2.56 13 5.35 2.02 6 9.8% -2.12 [-4.25, 0.01]
Kobayashi et al (2003) 2 0.94 14 2.73 2.58 14 14.3% -0.73 [-2.17, 0.71]
Trippel et al (2017) 1.45 1.43 43 1.42 0.59 19 21.2% 0.03 [-0.47, 0.53]
Total (95% CI) 202 151 100.0% -0.93 [-1.82, -0.05]
Heterogeneity: Tau² = 0.90; Chi² = 19.34, df = 8 (P = 0.01); I² = 59%
Test for overall effect: Z = 2.06 (P = 0.04)
-4 -2 0 2 4
Favours [experimental] Favours [control]

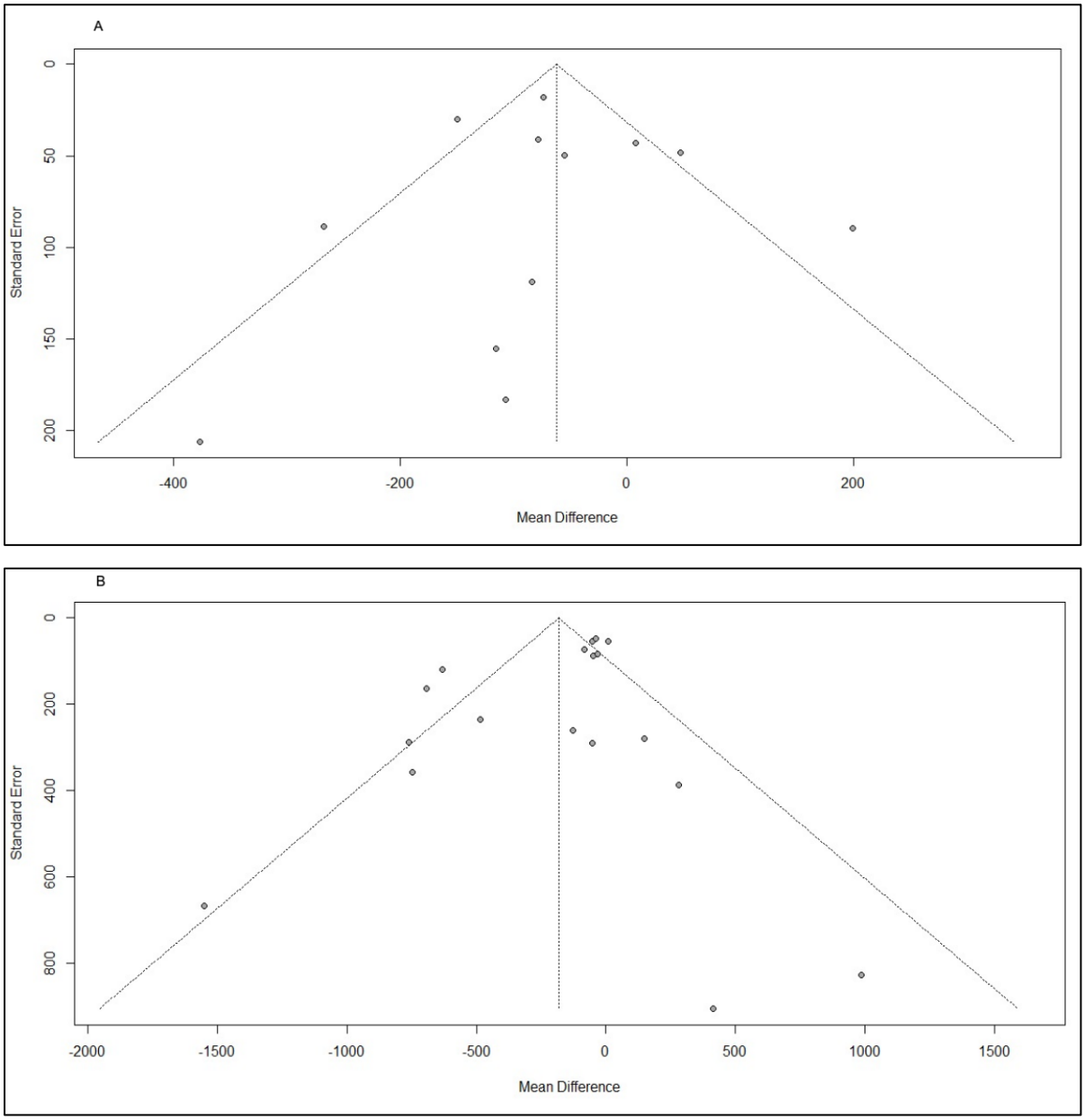
Box 1

Pubmed		
1	Heart Failure	**(Heart Failure[mh]** OR Heart Failure[tw] OR Cardiac Failure[tw] OR Heart Decompensation[tw] OR Right-Sided Heart Failure[tw] OR Right Sided Heart Failure[tw] OR Myocardial Failure[tw] OR Congestive Heart Failure[tw] OR Left-Sided Heart Failure[tw] OR Left Sided Heart Failure[tw])
2	Exercise	**(Exercise[mh]** OR Exercise*[tw] OR Physical Activit*[tw] OR Physical Exercise*[tw] OR Acute Exercise*[tw] OR Isometric Exercise*[tw] OR Aerobic Exercise*[tw] OR Exercise Training*[tw] OR Training, Exercise*[tw] OR High-Intensity Interval Training[mh] OR High Intensity Interval Training[tw] OR High-Intensity Interval Trainings[tw] OR High-Intensity Intermittent Exercise*[tw] OR Sprint Interval Training*[tw] OR Resistance Training[mh] OR Resistance Training[tw] OR Strength Training[tw] OR Weight-Lifting Strengthening Program[tw] OR Weight Lifting Strengthening Program*[tw] OR Weight-Lifting Exercise Program[tw] OR Weight Lifting Exercise Program*[tw] OR Weight-Bearing Strengthening Program*[tw] OR Weight Bearing Strengthening Program[tw] OR Weight-Bearing Exercise Program[tw] OR Weight Bearing Exercise Program*[tw] OR Tai-ji[mh] OR Tai Chi[tw] OR Tai Ji Quan[tw] OR Taiji[tw] OR Taijiquan[tw] OR T'ai Chi[tw] OR Tai Chi Chuan[tw] OR Circuit-Based Exercise[mh] OR Circuit Based Exercise[tw] OR Circuit Training[tw] OR Circuit-Based Exercises[tw] OR Cardiac Rehabilitation[mh] OR Cardiac Rehabilitation*[tw] OR Cardiovascular Rehabilitation*[tw] OR Plyometric Exercise[mh] OR Plyometric Exercise[tw] OR Plyometric Drill*[tw] OR Plyometric Exercises[tw] OR Plyometric Training*[tw] OR Stretch Shortening Cycle Exercise[tw] OR Stretch Shortening Drill[tw] OR Stretch Shortening Exercise[tw] OR Stretch-Shortening Cycle Exercise*[tw] OR Stretch-Shortening Drill*[tw] OR Stretch-Shortening Exercise*[tw])
3	Brain Peptide Natriuretic	**(Natriuretic Peptide, Brain[mh]** OR BNP-32[tw] OR BNP 32[tw] OR Brain Natriuretic Peptide-32[tw] OR Brain Natriuretic Peptide 32[tw] OR Natriuretic Factor-32[tw] OR Natriuretic Factor 32[tw] OR BNP Gene Product[tw] OR Type-B Natriuretic Peptide[tw] OR Type B Natriuretic Peptide[tw] OR Natriuretic Peptide Type-B[tw] OR Natriuretic Peptide Type B[tw] OR Nesiritide[tw] OR Brain Natriuretic Peptide[tw] OR B-Type Natriuretic Peptide[tw] OR Natrecor[tw])
4	Troponin	**(Troponin[mh]** OR Troponin*[tw] OR Troponin complex[tw])
5	C-Reative Protein	**(C-Reactive Protein[mh]** OR C-Reactive Protein[tw] OR "C Reactive Protein"[tw]
6	Cytokines	**Cytokines[mh]** OR Cytokines[tw])
7	Search	**(#1 AND #2) AND (#3 OR #4 OR #5 OR #6)**

Supplementary Figure 1



Supplementary Figure 2



Supplementary Table 1 Information regarding adverse events, dropouts, and exercise session compliance for the included studies

Study	Adverse events	Dropouts	Compliance
Abolahrari-Shirazi et al, 2018*	*Combined training group* - Angina pectoris during treadmill exercise, relieved after sublingual nitroglycerin (n=2). *Endurance training group* - Severe hypotension, normalized after discontinuing exercise (n=1) - Respiratory problem not related to exercise training (n=1).	*Combined training group* (n=2) *Endurance training group* (n=2) *Control group* (n=1)	Not reported
Adamopoulos et al, 2002	Not reported	Not reported	Not reported
Ahmad et al, 2014 (Biomarker Substudy HF ACTION Trial)	Not reported	Not reported	Not reported
Aksoy et al, 2015*	No adverse effect was detected during the training period.	*Intermittent aerobic group* (n=4) *Continuous aerobic group* (n=4) *Control group* (n=4)	Not reported
Butterfield et al, 2008	Not reported	*Combined training group* (n=2)	Not reported
Butts et al, 2018	Not reported	Not reported	60% completed at least 12 days of exercise per month for the 3-month intervention
Byrkjeland et al, 2011	The exercise training program was well tolerated and no complications occurred.	*Exercise group* (n=4)	95% of compliance to the exercise
Conraads et al, 2007	Not reported	Not reported	Not reported
De Meirelles et al, 2014	Not reported	Not reported	Not reported
Eleuteri et al, 2013	No adverse events occurred during training sessions.	Not reported	Negligible percentage of non-adherence to the prescribed training sessions (< 1%)
Erbs et al, 2010	*Exercise group* - Atrial fibrillation (17%) *Control group* - Atrial fibrillation (5%) - Sudden cardiac death (n=1)	*Exercise group* (n=1) *Control group* (n=1)	Not reported
Fernandes-Silva et al, 2017	None clinically relevant cardiovascular symptom during the study was reported.	*Exercise group* (n=9) *Control group* (n=3)	At least 70% of compliance
Fu et al, 2013*	Not reported	*Aerobic interval Group* (n=1) *Moderate continuous group* (n=2) *Control group* (n=2)	*Aerobic interval group* (93.3%) *Moderate continuous group* (86.7%) *Control group* (86.7%)

Gademan et al, 2013	Not reported	No dropouts in exercise and control groups	Not reported
Gary et al, 2011	There were no serious adverse events in any study participant.	Not reported	83% and 99% of adherence for walking sessions and resistance exercises, respectively
Guazzi et al, 2012	Not reported	Not reported	Not reported
Jónsdóttir et al, 2006	No training related adverse events were reported	*Control group* (n=2)	Not reported
Kobayashi et al, 2003	All patients completed the protocol without exacerbation of heart failure.	Not reported	Not reported
Lima et al, 2010	No adverse events during exercise training, such as exertional hypotension, congestive symptoms, or other signs of instability that might suggest decompensated CHF.	*Exercise group* (n=3)	94.9% of compliance
Linke et al, 2005	No death or cardiac decompensation occurred, and none of the patients was admitted to the hospital during the study period.	*Exercise group* (n=1) *Control group* (n=1)	Not reported
Malfatto et al, 2009	Not reported	Not reported	Not reported
Meyer et al, 2004	Not reported	Not reported	Not reported
Nilsson et al, 2010	The exercise program was well tolerated, with no complications during exercise.	*Exercise group* (n=2) *Control group* (n=2)	Not reported
Norman et al, 2012	Not reported	*Exercise group* (24-week) (n=2)	73% of adherence over the 24-week period to the exercise sessions
Parrinello et al, 2009	Not reported	Not reported	Not reported
Passino et al, 2006	*Exercise group* - Stroke (n=1) *Control group* - Hospitalization for decompensation (n=2)	*Exercise group* (n=3) *Control group* (n=7)	Not reported
Passino et al, 2008	*Control group* - Hospitalization for decompensation (n= not reported)	*Exercise group* (n=2) *Control group* (n=5)	Not reported
Sandri et al, 2012* (LEICA Study)	No serious adverse events occurred.	No dropouts occurred	Nearly 100% of adherence to training program
Sarullo et al, 2006	No significant cardiovascular events occurred during the training sessions. Sporadic supraventricular and ventricular premature contractions during exercise and recovery in the training group (n=6).	No dropouts occurred	93% of compliance (range 81–100%)
Stevens et al, 2015	Not reported	*Exercise group* (n=3) *Control group* (n=3)	93% of compliance to the exercise sessions (range 73%-100%).
Trippel et al, 2017 (Ex-DHF pilot study post hoc analysis)	No serious adverse events occurred. *Exercise training group* - Adverse events during or immediately after exercise occurred without clinical relevance (n=11). - Events with suspected cardiovascular background: brief episodes of palpitations (n=2), dyspnea (n=3), and mild musculoskeletal discomfort (n=9) during exercise.	*Exercise group* (n=2) *Control group* (n=1)	*Exercise group:* 34% participated in > 90% of exercise sessions, 52% in 70% to 90%, and 14% in < 70%.

Van Dissel et al, 2009	No patient experienced a cardiovascular event that occurred during or within 3 hours after training. *Exercise group* - Minor exercise related injuries (knee sprain, mild palpitations or minor head injury) (n=3). - At follow-up CPET, a self-limiting supraventricular arrhythmia during the recovery phase and low-dose β-blocker initiated (n=1). - Sporadic multiform ventricular premature complexes during exercise and recovery, treated conservatively (n=1).	*Exercise group* (n=3) *Control group* (n=3)	Thirteen (> 75%) of the 17 patients exercised at or above the target training level of 2 ¼ hours/week.
Wisløff et al, 2007*	No adverse effects were detected.	*Moderate continuous group* (n=1)	*Moderate continuous group:* 92±2% *Aerobic interval group*: 95±3% of the scheduled training sessions

CPET: Cardiopulmonary exercise testing; CHF: Chronic heart failure; Ex-DHF: Exercise training in diastolic heart failure.

* randomized between two exercise groups, besides control group.

ARTIGO 2

Title: Functional training versus strength training to improve peak oxygen consumption and quality of life in individuals with heart failure: a randomized clinical trial

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Abbreviated title: Functional training program for heart failure
Key words: Heart failure, Exercise, Functional training, Cardiopulmonary exercise capacity, Quality of life
Word Count: 250 words (Abstract)
2765 words (Introduction, Method, Results, Discussion)
References: 33
Tables: 2
Figures: 1
Footnotes: [a]T2100, General Electric, Wisconsin, USA, speed 0-22 km/h [0-13.5 mph], grade 0–26%. [b]G*Power program, version 3.1.92. [c]SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA)
eAddenda:
Ethics approval: The Hospital de Clínicas de Porto Alegre (HCPA) scientific committee and research ethics commission approved this study. All applicable institutional and governmental regulations concerning the use of human volunteers were followed. All participants gave written informed consent before data collection began.
Competing interests: Nil

Source(s) of support: The study has been funded by FIPE (Fundo de Incentivo à Pesquisa e Eventos, Hospital de Clinicas de Porto Alegre), IATS (Instituto de Avaliação de Tecnologia em Saúde) and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico). DMN receive doctoral funding support from CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior). PMB receives post-doctoral fellowship funding support from CAPES. BDS and NC receive research productivity grant and support from the CNPq foundation. Such funding agencies do not have any roles regarding the design of the study, data collection, analysis and interpretation of data, or in writing the manuscript.

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ABSTRACT

Questions: Could functional training improve peak oxygen consumption (VO_2) and quality of life of individuals with heart failure (HF)? Could functional training improve functionality, endothelial function, and enhance muscle mass and strength of individuals with HF? **Design**: Randomized, parallel-design, examiner-blinded, clinical trial with concealed allocation, intention-to-treat and per protocol analysis. **Participants:** Twenty-seven participants with HF, in regular follow-up at a single tertiary hospital. **Intervention:** Participants were randomly allocated to an experimental group (functional training) or a comparator group (strength training), to perform a 12-week supervised physical training. **Outcomes:** Primary outcomes were peak VO_2 and quality of life. Secondary outcomes included functionality (Duke activity status Index and gait speed test); peripheral and inspiratory muscular strength; endothelial function, and lean body mass. **Results:** In intention-to-treat analysis, the comparison within groups showed an increase in peak VO_2 by 1.4 (SD 3.2) and 1.5 (SD 2.5) ml/kg per minute in experimental and comparator group, respectively (p= 0.011); quality of life decreased by 13.7 (SD 15.0) and 12.0 (SD 28.1) points in experimental and comparator group, respectively (p= 0.001). Duke activity status Index and gait speed were also increased at the end of the training protocol in both groups, but no difference was observed between groups. There were no within or between-group differences observed for the remainder secondary outcomes. All participants completed the study without any serious adverse events. **Conclusions:** Functional and strength training are equally safe and effective in improving peak VO_2, quality of life, and functionality in individuals with HF. **Trial registration:** NCT03321682.

INTRODUCTION

Reduced exercise tolerance is a hallmark symptom of heart failure (HF) and it is associated with increased disability and mortality[1]. The mechanisms underlying exercise intolerance are considered multifactorial, and include central and peripheral factors[2; 3]. The sedentary lifestyle adopted by individuals with HF leads to peak oxygen consumption (VO_2) reductions and poor quality of life[4]. Individuals with HF have a 30% decreased ability to perform activities of daily living compared to healthy individuals, which has been attributed to reduced muscle mass and decreased VO_2[5]. Recent evidence suggests that exercise-based cardiac rehabilitation improves quality of life and functional capacity[6]. However, activities of daily living require a combination of endurance and strength, and aerobic training alone could not improve muscle strength[7]. Particularly, strength training does not usually represent the movements performed during routine daily activities since it does not include exercises using coordinated and multiplanar movement patterns or incorporate multiple joints and dynamic tasks[8].

In this context, functional training may be a potential effective nonpharmacological therapy for individuals with HF. This modality of physical training consists of integrated movements of the body in several planes that involve joint acceleration and deceleration, stabilization, strength, and neuromuscular efficiency[9]. In fact, functional training, sometimes called neuromotor exercise training, is a recommendation of the American College of Sports Medicine for apparently healthy adults of all ages[10]. However, the effectiveness of functional training in chronic diseases has not been established.

Studies addressing functional training basically focused on assessing functionality in an elderly population in terms of walking capacity[11], mobility[12], and prevention of falls[13]. Functional training could potentially improve peak VO_2 since it includes an aerobic component. Studies related to functional training published to date did not include peak VO_2 as an outcome, and some aspects such as volume, performance patterns, and progression of this type of training remain unknown.

The primary objective of the present study was to compare the effects of functional training versus strength training on peak VO_2 and quality of life of individuals with HF. Secondary objectives were to evaluate the: (1) effects of functional training versus

strength training on functionality, muscle strength, endothelial function, and lean body mass; (2) safety of a functional training program in individuals with HF.

Therefore, the research questions for this randomized trial were:

1. Could a new approach of physical training - functional training - be used to improve peak VO_2 and quality of life of individuals with HF?

2. Could functional training improve functionality, endothelial function, muscle mass and muscle strength of individuals with HF?

METHOD

Design

This is a randomized, parallel-design, 1:1 ratio allocation, examiner-blinded, clinical trial with concealed allocation, previously described in details[14]. This clinical trial is reported in accordance with CONSORT guidelines[15].

Participants

Individuals of both sexes, aged ≥ 40 years, were recruited from the outpatient cardiology clinic of Hospital de Clínicas de Porto Alegre (HCPA), a tertiary public hospital in southern Brazil.

The inclusion criteria were: clinically stable HF (ischemic and non-ischemic) for at least three months before randomization, diagnosed according to clinical records; New York Heart Association (NYHA) functional classes II-III, with slight to marked limitation of physical activity, respectively[16]; left ventricular ejection fraction equal or less than 45%; and optimized pharmacological treatment[16]. Individuals were excluded if they were enrolled in another clinical trial involving physical training protocols or in regular practice of physical exercise in the last three months; decompensated HF; presence of acute myocardial infarction and/or cardiac surgery in the previous six months; severe valvular heart diseases and/or uncontrolled cardiac arrhythmias; asymmetric septal hypertrophic cardiomyopathy with dynamic obstruction in the outflow pathway; musculoskeletal disorders limiting the execution of the protocol exercise program; impaired cognitive status that compromise the understanding and the execution of the study protocols.

Intervention

The participants were randomly allocated either to an experimental group (functional training group, FTG) or to an active comparator group (strength training group, STG), each training lasting 12 weeks. Participants underwent physical training three times per week, totaling 36 sessions. At each phase of 12 sessions, the exercises were modified and the participants were encouraged by the main researcher, a physiotherapist, to exercise at high performance (time or number of repetitions) and to progressively increase the difficulty of each exercise. Exercises and periodization model for both physical trainings were previously described[14].

Outcome measures

The outcomes were assessed at baseline, after provision of written informed consent, but before allocation to one of the study groups, and at the end of the 12 weeks. Baseline demographic and clinical information, such as age, sex, HF etiology, left ventricle ejection fraction and NYHA functional class, were obtained from electronic health records.

Primary outcomes:

Peak VO_2 was measured in cardiopulmonary exercise testing with expired gas analysis and performed on a treadmill[a]. Peak VO_2 (ml/kg per minute) was set to the highest 20 sec averaged value reached during the test. Maximality criteria are defined by a respiratory exchange ratio greater than or equal to 1.05[17].

Quality of life was assessed by the Minnesota Living with Heart Failure Questionnaire (MLHFQ), a disease specific instrument. Total score ranges from zero to 105 points, with low scores reflecting a better health-related quality of life[18].

Secondary outcomes:

Functionality was evaluated by the Duke activity status Index (DASI) and the gait speed test. The DASI ranges from zero to 58.2 points. A higher score represents a better functional capacity[19]. The gait speed test was performed in a corridor of 20 meters. The participant walked at his own pace, without running, and the time spent in the central 10 meters of the corridor was determined. Then, the ratio between distance and time (meters/second) was calculated[20].

The hand grip dynamometer was used to evaluate peripheral muscle strength[21]. Strength values were calculated in kilograms, and the average of three attempts for the dominant hand, performed with a one-minute interval between measures was considered. Inspiratory muscle strength or maximal inspiratory pressure (cmH_2O) were evaluated by manovacuometry[22]. At least three reproducible maneuvers were performed using a digital pressure manometer. For data analysis, the highest value was recorded as long as it did not exceed the second highest value by 10%.

Noninvasive measurements of endothelial function were obtained by flow mediated dilation (FMD) and nitroglycerine-induced vasodilation of the brachial artery using two-dimensional ultrasound equipment, in accordance with published guidelines[23], and always by the same trained operator. The FMD method involves ultrasound arterial imaging in two conditions: at rest (baseline) and during reactive hyperemia, after a five-minute arterial occlusion. Nitroglycerine-induced vasodilation, an index of endothelium-independent vasodilation, was assessed five minutes after the administration of a single sublingual 0.4 mg dose of nitroglycerine. Both FMD[24] and nitroglycerine-induced vasodilation[25] were calculated as the percent change in peak vessel diameter from the baseline value, using [(peak diameter - baseline diameter)/baseline diameter] x 100.

Lean body mass was evaluated by arm muscle circumference, which was obtained from arm circumference and tricipital skinfold measurements using the tape measure and adipometer, respectively. The arm muscle circumference was calculated as: arm muscle circumference (cm) = [arm circumference (cm) – (0.314 x tricipital skinfold (mm)][26].

Adherence to the exercise programs were evaluated considering exercise program attendance and was defined as reaching at least 80% of the recommended or prescribed exercise sessions[27].

Data analysis

To calculate the sample size, a statistical analysis program[b], was used. Considering a power of 80%, a significance level of 5%, a correlation of 0.7 among repeated measures, and a small effect size *f* of 0.2 for the peak VO_2, a total sample size of 32 participants was estimated, including 16 in each study group. To account for a 20% estimated participant loss or refusal rate, we defined that 19 participants should be

enrolled in each group, totalizing 38 participants. The calculated sample size was not obtained because the trial was interrupted due to the COVID-19 pandemic.

Descriptive statistical analysis using mean and standard deviation was used initially, followed by testing of normality by the Shapiro-Wilk test. Fisher's exact test, Yates's chi-squared test, and Student's t test were used to compare groups at baseline. Differences within groups (mean and standard deviations) and between groups (mean and 95% CIs) were assessment before and after the 12-week intervention period. For both analyses, generalized estimation equations (GEE) were used, followed by the Bonferroni's post hoc test.

Intention-to-treat analysis was performed with all randomized participants for the primary and secondary outcomes. Per protocol analysis was performed for the same outcomes with participants who were classified as adherent to exercise programs (adherence ≥ 80%). Analyses were performed using commercial software[c]. In all tests, and a significance level of $p < 0.05$ was adopted.

RESULTS

Flow of participants, therapists, centres through the study

Twenty-seven participants were randomized to the experimental group, FTG (n= 13) or the active comparator group, STG (n= 14). The flow of participants through the study is presented in Figure 1. The baseline characteristics of the participants are presented in Table 1. Overall, participants were 60.4 years old (SD 7), predominantly male (66.7%), caucasian (70.4%) and overweight or obese (40.7%). Non-ischemic cardiomyopathy was the most common etiology for HF (51.9%), while hypertension was the most prevalent comorbidity (55.6%), followed by diabetes (51.8%). Almost 30% of participants had an implantable cardioverter-defibrillator or a cardiac resynchronization therapy device. All participants were taking beta-blockers and most of them (85.2%), angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers. There were no baseline differences between groups, except for active smoking (p= 0.043), which was more prevalent in FTG (28.6%) than in STG (0%).

A qualified physiotherapist, specialized in sports sciences, provided the intervention to both the experimental and comparator groups throughout the study. In

addition, the physical therapist received further training in the specific exercise programs for this study. The exercise sessions took place at the institutional Center for Clinical Research at the institution, which is a public, academic tertiary hospital.

Compliance with the study protocol

After randomization and before the final assessment, four participants in the FTG and three participants in the STG withdrew from the intervention and final assessment of their clinical outcomes. In the FTG, the withdrawals were due to loss of interest (n= 2), implantable cardioverter-defibrillator procedure (n= 1), and restrictions imposed by COVID-19 (n= 1). In the STG, the withdrawals were due to loss of interest (n= 2) and heart transplant (n= 1). Baseline values of clinical outcome measures for the patients who discontinued study participation were included in the intention to treat analysis.

Considering adherence to training programs, attendance rates were similar between groups: 72.0% (SD 33.1) versus 71.6% (SD 27.3), for FTG and STG, respectively. All participants completed the study without any serious adverse events. In the FTG, there was only one episode of low back pain reported. Non-serious adverse events in the STG included hypoglycemia (n= 1), gout exacerbation (n= 3), and nausea (n= 3).

Effect of intervention on clinical outcomes

The effects of both interventions on primary and secondary outcomes are shown in Table 2. The intention to treat analysis showed an improvement in peak VO_2 (p group= 0.988, p time= 0.011 and p interaction= 0.921) and in quality of life (p group= 0.067, p time= 0.001 and p interaction= 0.921) in both study groups after 12 weeks. Peak VO_2 increased similarly by 1.4 (SD 3.2) and 1.5 (SD 2.5) ml/kg per minute in functional and strength training groups, respectively. The quality of life score decreased by 13.7 (SD 15.0) points in the FTG and 12.0 (SD 28,1) points in the STG. In per protocol analysis, similar results were observed. Peak VO_2 (p group= 0.716, p time < 0.001 and p interaction= 0.895) and quality of life (p group= 0.354, p time= 0.013 and p interaction= 0.924) improved in both study groups after 12 weeks of training. An increase of 2.6 (SD 2.5) and 2.7 (SD 2) ml/kg per minute for peak VO_2 was observed in FTG and STG, respectively. The quality of life score decreased by 13.9 (SD 9.8) points in FTG and 12.8 (SD 29.2) points in STG.

Considering the DASI, the intention to treat analysis showed an improvement in functionality in both study groups after 12 weeks of training (p group= 0.482, p time= 0.019, p interaction= 0.947); and an increase of 6.5 (SD 12.1) and 5.2 (SD 13.2) points was observed for FTG and STG. The gait speed also increased in both groups after 12 weeks of training (p group= 0.913, p time= 0.002, p interaction= 0.576); an increase of 0.2 (SD 0.3) m/s was demonstrated in FTG and STG. The per protocol analysis showed an improvement only in gait speed in both study groups after 12 weeks of training (p group= 0.477, p time= 0.005, p interaction= 0.349); an increase of 0.2 (SD 03) and 0.3 (SD 0.4) m/s was demonstrated in demonstra-te FTG and STG, respectively.

There were no differences within and between groups in the intention to treat and per protocol analysis for peripheral muscle strength, maximal inspiratory pressure, endothelial function, and lean body mass.

DISCUSSION

To our knowledge, this is the first randomized clinical trial aimed at evaluating the effects of functional training in individuals with HF. We compared functional training to strength training due to similarities between both physical modalities, and because the latter is traditionally recommended by the *American College of Cardiology Foundation* and the *American Heart Association* as a non-pharmacological therapeutic approach in HF[28].

Our study demonstrated that both functional training and strength training, performed at a moderate intensity, increased peak VO_2, and improved quality of life, and functionality after a 12-week exercise program. Sperlich et al[29] found an increased in peak VO_2 of overweight women, after 9 weeks of both, high-intensity functional training alone or in combination with low-intensity functional training. The quality of life was also improved by both physical trainings. However, the population studied was different from ours. Among patients with HF, the HF-ACTION (Heart Failure and a Controlled Trial Investigating Exercise Training Results) showed a median percentage improvement just of 4% in peak VO_2 in the aerobic training group versus usual care, after 12 weeks of intervention[30]. Conversely, we demonstrated an improvement of 10% in peak VO_2 in both groups, which is customarily used as a clinically relevant improvement.

Considering measures of functionality, we demonstrated increments in the DASI and gait speed in both training groups after 12 weeks, although no difference was observed between exercise modalities. Corroborating our findings, Krebs et al[30] demonstrated greater maximum and average gait speed performed by elders when comparing six weeks of functional training versus strength training. Also, Vreede et al[31] showed an increased in the ability of community-living old people to perform daily tasks after 12 weeks of both functional-task exercise program and resistance training, however, with a greater magnitude observed in the functional training group, which is different from our results, but the population studied was also different.

In the present study, the functional training was performed with a strength component and did not demonstrate changes on muscle strength. The strength training also did not lead to changes on muscle strength. A systematic review performed by Liu et al[8] examined the effects of functional training on muscle strength, physical functioning, and activities of daily living in old adults. Despite a large variability of exercise prescriptions, studies demonstrated that functional training was associated with improved mobility and activities of daily living. Muscle strength was increased when functional training was performed with strength component. When functional training was performed without a strength component, the findings did not favor functional training. These findings may indicate a superiority of strength training over functional training in the field of muscle strength, but not over the ability to perform activities of daily living. It reinforces the principle of specificity of training, which means that training in a specific activity is the best way to maximize the performance in that specific activity[32].

Some limitations of this study should be addressed. First, we could not complete the sample size since the study had to be finished earlier due to the COVID-19 pandemic. Second, participants' difficulties in commuting to the clinical research center related to distance and costs may have reflected on adherence to physical training programs. Finally, we believe that hand grip may not have been the best measure to assess peripheral muscle strength, since a greater emphasis was placed on lower limb exercises.

In conclusion, our study demonstrated that functional training is safe and effective in improving oxygen consumption, quality of life, and functionality of individuals with HF, as strength training. These findings suggest that functional training may be a

promising, exercise-based strategy for the treatment of HF. Future research is needed to better explore its effects in special subgroups of patients with HF.

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Figure legends:

Figure 1. Design and flow of participants through the trial.

Table 1. Baseline demographic and clinical characteristics of participants.

Characteristic	**Total sample (n = 27)**	**FTG (n = 14)**	**STG (n = 13)**
Age (*years*)	60.4 (7)	62.8 (4.9)	57.8 (8.2)
Men	18 (66.7)	9 (64.3)	9 (69.2)
Ethnicity			
Caucasian	19 (70.4)	11 (78.6)	8 (61.5)
Black	6 (22.2)	3 (21.4)	3 (23.1)
Other	2 (7.4)	0 (0)	2 (15.4)
BMI (kg/m^2)	29.4 (6.3)	28.9 (6.0)	30 (6.8)
Heart failure etiology			
Ischemic	13 (48.1)	8 (57.1)	5 (38.5)
Non ischemic	14 (51.9)	6 (42.9)	8 (61.5)
NYHA			
II	21 (77.8)	11 (78.6)	10 (76.9)
III	6 (22.2)	3 (21.4)	3 (23.1)
LVEF	28.9 (8.5)	29.7 (9.6)	28 (7.4)
Comorbidities			
Diabetes	14 (51.8)	6 (42.9)	8 (61.5)
Hypertension	15 (55.6)	6 (42.9)	9 (69.2)
COPD	3 (11.1)	1 (7.1)	2 (15.4)
ICD/CRT	8 (29.6)	4 (28.6)	4 (30.8)
Osteomuscular disorders	6 (22.2)	3 (21.4)	3 (23.1)
Active smoking	4 (14.8)	4 (28.6)	0 (0)
Drug Therapy			
Beta-blockers	27 (100)	14 (100)	13 (100)
ACEI/ARB	23 (85.2)	12 (85.7)	11 (84.6)
Digoxin	13 (48.1)	7 (50)	6 (46.2)
Nitrates	8 (29.6)	3 (21.4)	5 (38.5)
Diuretics	26 (96.3)	13 (92.9)	13 (100)
Antiplatelet agent and/or anticoagulation	19 (70.4)	10 (71.4)	9 (69.2)
Statins	16 (59.3)	10 (71.4)	6 (46.2)

Data are expressed as means (SD) or n (%). Comparisons (FTG: Functional training group *vs.* STG Strength training group). ACEI: Angiotensin-Converting Enzyme Inhibitor. ARB: Angiotensin II Receptor Blocker. BMI: Body Mass Index. COPD: Chronic Obstructive Pulmonary Disease. CRT: Cardiac Resynchronization Therapy. ICD: Implantable Cardioverter-Defibrillator. LVEF: Left Ventricular Ejection Fraction. NYHA: New York Heart Association.

Table 2. Mean (SD) values for study outcomes in each group, mean (SD) difference within groups, and mean (95% CI) difference between groups.

Intention-to-treat analysis							
Outcomes	Groups				Difference within groups		Difference between groups
	Week 0		Week 12		Week 12 minus Week 0		Week 12 minus Week 0
	FTG (n = 14)	STG (n=13)	FTG (n = 14)	STG (n = 13)	FTG	STG	FTG minus STG
Primary outcomes:							
$VO_{2\,peak}$ (*ml/kg per minute*)	16.9 (2.9)	16.8 (4)	18.6 (4.8)	18.6 (5.5)	1.4 (3.2)	1.5 (2.5)	0.12 (-2.5 to 2.7)
Quality of life score (*points*)	25.8 (14.8)	33.8 (23.8)	10.3 (7.8)	19.0 (15.1)	-13.7 (15.0)	-12.0 (28.1)	1.7 (-19.4 to 22.8)
Secondary outcomes:							
Duke activity status Index (*points*)	28.8 (12.4)	26.2 (13.2)	34.5 (12.3)	33.0 (11.1)	6.5 (12.1)	5.2 (13.2)	-1.3 (-13.2 to 10.6)
Gait speed *(m/s)*	1.6 (0.3)	1.5 (0.2)	1.7 (0.3)	1.8 (0.3)	0.2 (0.3)	0.2 (0.3)	0.05 (-0.3 to 0.4)
Hand grip strength (*kg*)	31.5 (10.3)	28.7 (9.4)	28.4 (9.1)	32.4 (9.4)	-2.7 (5.5)	1.9 (4.8)	4.6 (-0.2 to 9.4)
Maximal inspiratory pressure (cmH_2O)	64.5 (31.2)	66.1 (32.3)	63.5 (31.0)	56.2 (11.5)	1.6 (33.0)	-10.2 (21.8)	-11.8 (-38.1 to 14.5)

Endothelial function:							
Flow-mediated dilation (%)	6.3 (5.5)	9.8 (3.9)	4.8 (5.1)	6.4 (4.4)	1.2 (9.5)	3.4 (5.1)	2.2 (-5.8 to 10.3)
Nitroglycerine-induced vasodilation (%)	11.8 (5.0)	17.2 (5.8)	14.1 (7.6)	16.1 (9.0)	1.5 (8.1)	-0.8 (11.4)	-2.3 (-13 to 8.3)
Arm muscle circumference (*cm*)	29.6 (3.7)	28.8 (4.4)	29.6 (6.9)	29.1 (4.0)	1.3 (5.8)	0.9 (2.6)	-0.4 (-5.1 to 4.2)

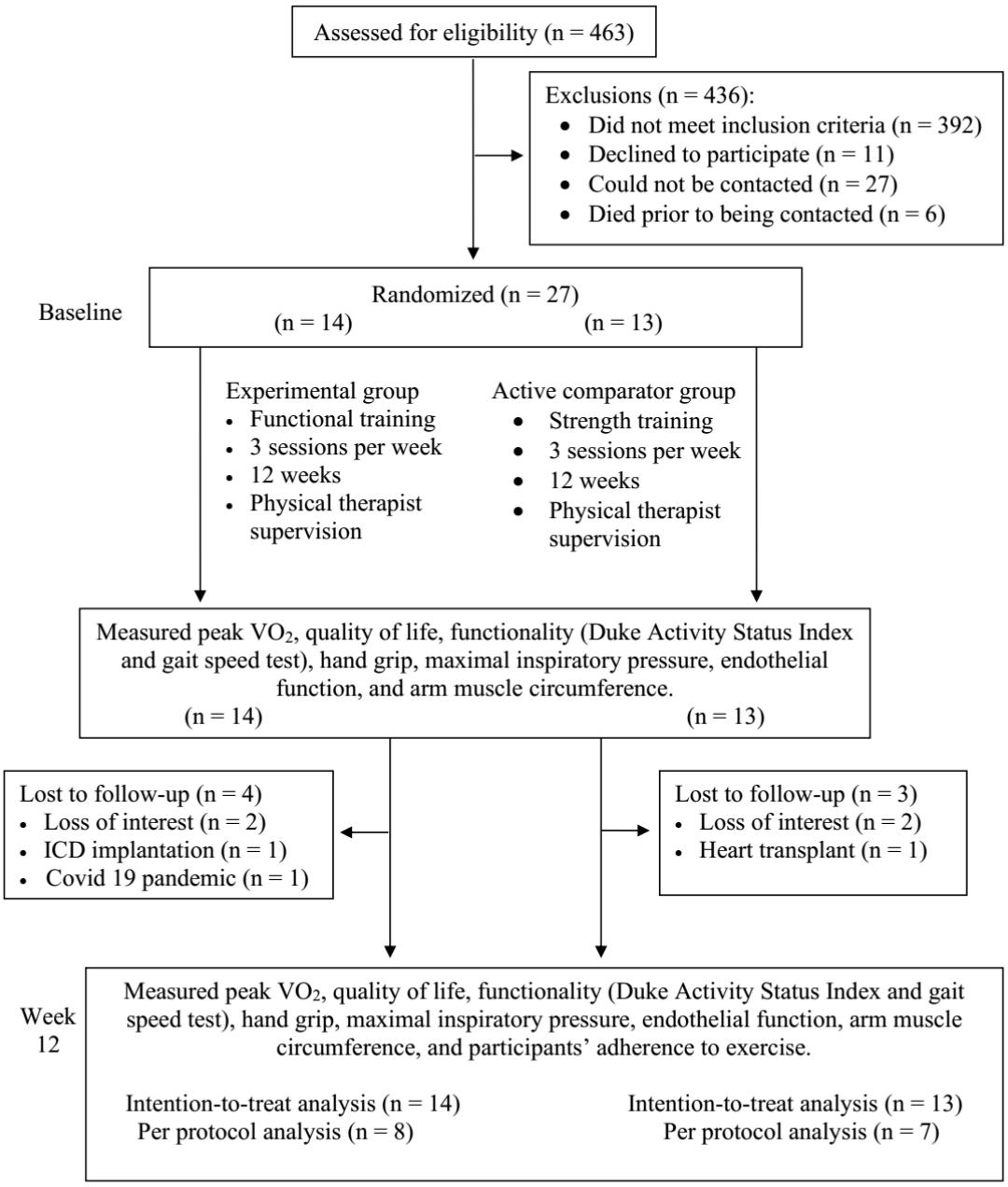
Per protocol analysis

	Groups				Difference within groups		Difference between groups
	Week 0		Week 12		Week 12 minus Week 0		Week 12 minus Week 0
	FTG (n = 8)	STG (n = 7)	FTG (n = 8)	STG (n = 7)	FTG	STG	FTG minus STG
Primary outcomes:							
VO_{2peak} (*ml/kg per minute*)	16.9 (3.1)	17.6 (4.8)	19.4 (4.7)	20.3 (5.5)	2.6 (2.5)	2.7 (2.0)	1.2 (-2.4 to 2.7)
Quality of life score (*points*)	22.2 (12.0)	27.3 (28.0)	8.4 (6.2)	14.4 (10.2)	-13.9 (9.8)	-12.8 (29.2)	1.0 (-22.6 to 24.6)
Secondary outcomes:							
Duke activity status Index (*points*)	31.3 (11.1)	33.3 (13.5)	34.3 (11.2)	38.7 (5.5)	2.9 (9.8)	5.3 (15.7)	2.4 (-11.9 to 16.7)
Gait speed (*m/s*)	1.5 (0.3)	1.6 (0.2)	1.7 (0.3)	1.9 (0.4)	0.2 (0.3)	0.3 (0.4)	0.2 (-0.2 to 0.5)
Hand grip strength (*kg*)	29.4 (11.1)	28.6 (8.0)	26.5 (8.3)	31.6 (9.7)	-2.9 (6.2)	3.0 (4.0)	-5.9 (0.02 to 11.7)
Maximal inspiratory pressure (cmH_2O)	61.9 (38.6)	67.9 (25.2)	67.1 (32.9)	57.4 (10.4)	5.2 (35.6)	-10.4 (22.9)	17.7 (-49.7 to 18.3)

Endothelial function:							
Flow-mediated dilation (%)	6.6 (6.4)	9.3 (3.3)	4.5 (5.8)	5.4 (4.4)	-2.1 (10.7)	-3.4 (5.7)	4.9 (-12.1 to 9.5)
Nitroglycerine-induced vasodilation (%)	12.0 (7.0)	15.7 (7.6)	13.1 (8.7)	13.5 (8.1)	-0.2 (8.8)	-3.5 (11.3)	-3.4 (-16.4 to 9.7)
Arm muscle circumference (*cm*)	27.7 (3.3)	28.2 (4.4)	28.2 (5.8)	28.7 (3.8)	0.6 (6.0)	0.5 (2.5)	-0.1 (-5.8 to 5.6)

FTG: Functional training group; STG: Strength training group.

Figure 1



ICD: Implantable Cardioverter-Defibrillator

CONCLUSÕES E CONSIDERAÇÕES FINAIS

O treinamento físico está associado à redução dos níveis de peptídeos natriuréticos, proteína C-reativa e citocinas inflamatórias (TNF-α, IL-1ß e IL-6). No entanto, ainda há lacunas na literatura com relação aos efeitos do treinamneto físico sobre outros biomarcadores, tais como as troponinas cardíacas. Embora haja uma grande diversidade nos protocolos de treinamento, foram destacados alguns aspectos relacionados à prescrição de exercícios para pacientes com IC.

Ainda no cenário do treinamento físico, demonstramos que o treinamento funcional, bem como o treinamento de força, é seguro e eficaz para melhorar o consumo de oxigênio, a qualidade de vida e a funcionalidade de indivíduos com IC. Esses achados sugerem que o treinamento funcional pode ser uma estratégia promissora no tratamento não-farmacológico da IC.

ANEXOS

Cardiopulmonary exercise capacity and quality of life of patients with heart failure undergoing a functional training program: Study protocol for a randomized clinical trial

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Abstract

Background: Exercise intolerance is a common finding in heart failure that generates a vicious cycle in which the individual starts to limit his activities even more due to progressive fatigue. Regular physical exercise can increase the cardiopulmonary exercise capacity of these individuals. A new approach to physical exercise, known as functional training, could improve the oxygen consumption and quality of life of patients with heart failure; however, there is no information about the effect of this modality of exercise in this patient population. This randomized trial will compare the effects of 36 sessions of functional training versus strength training in heart failure patients.

Methods: This randomized parallel-design examiner-blinded clinical trial includes individuals of both sexes aged ≥ 40 years receiving regular follow-up at a single academic hospital. Subjects will be randomly allocated to an intervention group (for 12-week functional training) or an active comparator group (for 12-week strength training). The primary outcomes will be the difference on cardiopulmonary exercise testing and quality of life from baseline to the 3-month time point in peak oxygen consumption assessed by the Minnesota Living with Heart Failure Questionnaire. Secondary outcome measures will include functionality assessed by the Duke Activity Status Index and gait speed test; peripheral and inspiratory muscular strength, assessed by hand grip and manovacuometry testing, respectively; endothelial function by brachial artery flow-mediated dilation; lean body mass by arm muscle circumference; and participant adherence to the exercise programs classified as a percentage of the prescribed exercise dose.

Discussion: The functional training program aims to improve the functional capacity of the individual using exercises that relate to his specific physical activity transferring gains effectively to one's daily life. In this context, we believe that that functional training can

increase the cardiopulmonary exercise capacity and quality of life of patients with heart failure. The trial has been recruiting patients since October 2017.

Trial registration: NCT03321682. Registered on October 26, 2017.

Keywords: Heart failure; Exercise; Functional training; Cardiopulmonary exercise capacity; Quality of life

Background

Exercise intolerance is a common finding in heart failure (HF) that generates a vicious cycle in which the individual starts to limit his activities even further due to progressive fatigue [1]. The mechanisms underlying exercise intolerance are generally considered multifactorial and include endothelial dysfunction. In patients with HF, improved endothelial dependent dilation as a result of exercise training is associated with increased exercise capacity, even in the absence of improved cardiac output [2]. Patients with HF, even when stable and compensated, experience a decline in functional capacity associated with a lower quality of life [3, 4]. Recent evidence suggests that exercise-based cardiac rehabilitation improves quality of life and functional capacity [5]. Despite the known benefits of physical training for patients with HF, the rates of adherence with recommended exercise are low, potentially limiting its ability to improve clinical outcomes [6].

In fact, a loss of strength and muscle mass, known as sarcopenia, is highly prevalent in this population and constitutes an important determinant of functional independence, hospitalization rates, and quality of life [7]. Patients with HF have a 30% decreased ability to perform activities of daily living (ADLs) compared to healthy individuals, which has been attributed to reduced muscle mass and decreased oxygen consumption (VO_2) [8]. In this context, strength training increases muscle torque and endurance, functional independence, and quality of life, reducing the morbidity of individuals with and those without cardiovascular disease [9]. The lower overload to the cardiorespiratory system related to strength training may be a safe and comfortable alternative for exercise prescription to patients with HF [10]. Recent meta-analyses have shown a significant increase in peak VO_2 in patients with HF as a clinical outcome of strength training [11, 12].

However, ADLs require a combination of endurance and strength, and aerobic training alone does not improve muscle strength [13]. In addition, traditional resistance/strength training does not ideally represent the movements performed during ADLs since it does not include exercises using coordinated and multiplanar movement patterns or incorporate multiple joints and dynamic tasks [14].

Functional training may be a potential effective nonpharmacological therapeutic intervention for patients with HF. Articles related to functional training published to date did not include peak VO_2 as an outcome, which makes this intervention innovative for patients with HF. Studies including functional training basically focused on assessing functionality in an elderly population in terms of walking capacity [15] and mobility [16]. This exercise method consists of integrated movements of the body in several planes that involve joint acceleration and deceleration, stabilization, strength, and neuromuscular efficiency (Figure 1).

The method aims to improve the functional capacity of the individual using exercises that relate to his specific physical activity, effectively transferring gains to one's daily life [14, 17]. In fact, functional training, sometimes called neuromotor exercise training, is a recommendation of the American College of Sports Medicine for apparently healthy adults of all ages [18]. Functional training could improve peak VO_2 since it also includes an aerobic component. However, some aspects such as volume, performance patterns, and progression remain unknown. Additionally, the effectiveness of exercise training in chronic diseases has not been established [14]. The choice of the strength group as an active comparator group was because this type of training does not increase peak VO_2 in the same magnitude as exercises with a larger cardiopulmonary component, as we expect in functional training. The primary objective of the present study is to compare the effects of functional training versus strength training on the cardiopulmonary exercise

capacity and quality of life of patients with HF. Secondary objectives are to evaluate the: (1) effects of functional training versus strength training on functionality, muscle strength, endothelial function, and lean body mass; (2) adherence of participants to both physical training protocols; and (3) safety of a functional training program.

Methods/Design

Study setting

This randomized parallel-design 1:1 ratio allocation examiner-blinded clinical trial is conducted at the Hospital de Clínicas de Porto Alegre (HCPA), a tertiary hospital in the city of Porto Alegre, Southern Brazil. The study was approved by the facility's institutional review board on August 8, 2017 (protocol no. 20170291). The study protocol adheres to the SPIRIT 2013 recommendations [19] (Additional file 1). The World Health Organization Trial Registration Dataset is provided herein (Additional file 2). Written informed consent is obtained from all patients before participation (Additional file 3).

Eligibility criteria

The study's inclusion and exclusion criteria are defined below.

Inclusion criteria

- Age equal to or older than 40 years.
- Clinically stable HF (ischemic and non-ischemic) for at least 3 months before randomization and diagnosed according to clinical records.
- New York Heart Association (NYHA) functional class II–III with slight to marked limitation of physical activity, respectively [20].
- Left ventricular ejection fraction (LVEF) equal to or less than 45%.

- Optimized pharmacological treatment [20].

Exclusion criteria

- Enrollment in another clinical trial involving physical training protocols.
- Regular practice of physical exercise of more than 150 minutes per week [21] in the last 3 months.
- Decompensated HF.
- Acute myocardial infarction and/or cardiac surgery for less than 6 months.
- Severe valvular heart diseases and/or uncontrolled cardiac arrhythmias.
- Asymmetric septal hypertrophic cardiomyopathy with a dynamic obstruction in the outflow pathway.
- Musculoskeletal disorders limiting completion of the protocol exercise program.
- Impaired cognitive status that compromises the understanding of the steps and completion of the study protocol.

Intervention

The participants are randomly allocated to a functional training program or a strength training program, each lasting 3 months. The exercise sessions are completed at the Center of Clinical Research at the HCPA. The patients perform the exercise training three times/week for a total of 36 sessions. Both physical exercise training programs are performed under the supervision of a physiotherapist who specialized in sports sciences. The exercises are performed individually or in pairs. Resting heart rate (HR) and blood pressure are measured with a validated digital automatic sphygmomanometer before and after each training session. The first two training sessions are earmarked for patients to become familiar with the exercises.

Each training session lasts approximately 50–60 minutes, consisting of an initial warm-up of 5 minutes, 35–45 minutes of functional or strength exercises, and 10 minutes of stretching and cool-down (Table 1).

Table 1. Phases of the sections and collection of exercises performed in training protocols

Functional Training Session	**Strength Training Session**	**Time**
Warm-up:	***Warm-up:***	5 minutes
Run on the trampoline	Stationary gait and calisthenics exercises	
Functional exercises:	***Strength exercises:***	35-45 minutes
Core strength	Shoulder abduction	
Agility and balance	Triceps extension	
Knee and hip dominance	Biceps curls, bench press	
Vertical pressure	Abdominals, calf raises	
Horizontal pressure	Leg extension, seated leg curl	
Horizontal and vertical pulling	Leg press and leg abduction	
Cool-down:	***Cool-down:***	10 minutes
Stretching exercises for lower limbs, upper limbs, and spine	Stretching exercises for lower limbs, upper limbs, and spine	

Functional training

Each phase of functional training includes a total of 10–12 different exercises. Prescribed movements consist of multi-joint exercises emphasizing major muscle groups and ADLs like sitting, standing up, pushing, and pulling. Unstable surfaces, cones, ladder

drills, elastic bands, kettlebells, dumbbells, steps, and Swiss balls are used in the training. Exercise intensity is self-paced, although the participants are encouraged by the physical therapist to exercise at high performance (time and number of repetitions) and progressively increase its performance or the difficulty of each exercise. A rest period between the series is determined by the time required for proper patient positioning and breath recovery. Indeed, the exercises are adjusted for each session depending on changes in functional and health status. The sequence of the functional exercises is designed to alternate strength exercises with agility training or strength exercises with aerobic conditioning as well as arm exercises with leg exercises always grouped in pairs or every three exercises. Running on the trampoline is performed as the warm-up and repeated at the end of the session before stretching exercises (Table 2).

Insert Table 2 here

Strength training

The strength training follows the recommendations for resistance training in individuals with cardiovascular disease by the American Heart Association [9]. The exercise protocol involves large muscle groups alternating their execution between the upper and lower limbs. Free weights (dumbbells, barbells, and ankle weights) and weight machines are used in the training. Two sets of 8–12 repetitions for the upper limbs and 12–15 repetitions for lower limbs are performed. The participants are encouraged by the physical therapist to perform a higher number of repetitions. The first two sessions are designed to determine the load of each exercise using the Borg scale (effort target of 3–4) and adapt the participant to the training. The progression of the exercises occurs at 4-week intervals.

Criteria for discontinuation and safety interventions

A participant may be discontinued from the study at the investigator's discretion for safety reasons. For any study subjects, an incident cardiovascular event, hospitalization, or severe health event during the intervention period are considered criteria to discontinue study participation. If typical thoracic pain, disabling dyspnea, and/or exercise-related syncope occur during the training session, the exercise intervention will be interrupted. Trained nursing staff at the clinical research center will provide clinical assessment and event-directed interventions accordingly. If necessary, immediate transfer to the hospital's emergency department will be performed.

Strategies for trial retention

During weekends, participants allocated to both groups receive phone calls to reinforce intervention session time and place. We use phone calls to inquire about any adverse events if a participant misses a session of any intervention arm. The phone call schedule will cease for participants declaring their withdrawal from the study.

Outcomes

The outcomes are assessed at baseline and after the provision of written informed consent but before allocation to one of the study groups. At the end of the 12-week period, the subject will be re-evaluated (Figure 2).

Patients' baseline demographic and clinical information including age, sex, HF etiology, left ventricle ejection fraction, and NYHA functional class are obtained from their electronic health records.

The primary outcome measures are cardiopulmonary exercise capacity and quality of life; the secondary outcomes include assessment of functionality, peripheral and inspiratory muscle strength, endothelial function, lean body mass, and participant adherence to exercise programs.

Measurement of primary outcomes

Cardiopulmonary exercise capacity

Cardiopulmonary exercise testing with expired gas analysis is performed on a treadmill (T2100, General Electric, WI, USA; speed 0–22 km/h [0–13.5 mph], grade 0–26%). A ramp protocol is used with a starting speed of 2.0 km/h or 2.5 km/h and a starting grade of 0%. Increments of 0.5 km/h per minute in speed and 1% per minute in grade were used to achieve fatigue within 8–12 minutes. During the test, gas exchanges are continuously measured breath-by-breath by a previously validated system (Quark CPET; COSMED, Rome, Italy).

Blood pressure is monitored every 3 minutes using a sphygmomanometer. HR is monitored using 12-lead electrocardiography (Quark C12x; COSMED) with electrode placement as described by Mason and Likar [22]. The test analyzes the ventilatory and metabolic variables. Peak VO_2 is set to the highest 20-sec average value reached during the test. Maximality criteria are defined by a respiratory exchange ratio greater than or equal to 1.05.

Quality of life

The Minnesota Living with Heart Failure Questionnaire, a disease-specific instrument used to assess quality of life, consists of 21 questions about limitations that are often associated with how HF prevents patients from living as they would like to.

Patients answer the questions as they related to the previous month. The total score is 0–105 points. A low score reflects a better health-related quality of life. The instrument is validated in Portuguese [23].

Measurement of secondary outcomes

Functionality

The Duke Activity Status Index is a 12-item questionnaire that assesses daily activities. Each item has a specific weight based on metabolic equivalents. The participants identify each of the activities that they can perform. The final score is 0–58.2 points. A higher score represents better functional capacity. The instrument is validated in Portuguese [24].

The gait speed test is used to evaluate and monitor the functional status and general health of a wide variety of populations. The method requires a 20-m corridor. The patient walks at his own pace, without running, and the time spent in the central 10 m of the corridor is determined. The ratio between distance and time (meters/second) will then be calculated [25].

Peripheral muscle strength

The hand grip dynamometer has been widely used to evaluate the nutritional status, functional, lateral dominance, and total strength of individuals always divided into groups by sex and age. Hand grip strength is assessed as recommended American Association of Hand Therapists [26] using a JAMAR® dynamometer (Sammons Preston, Inc., Bolingbook, IL, USA). The strength values in kilograms will be calculated as the average of three attempts for the dominant hand performed at 1-minute intervals between measurements.

Inspiratory muscle strength

Manovacuometry assesses inspiratory muscle strength or maximal inspiratory pressure (MIP) by maintaining a maximum negative pressure for at least 1 second after a forced expiration to residual volume against an occluded airway as recommended by the American Thoracic Society. At least three reproducible maneuvers must be performed using a digital pressure manometer (MVD300; Globalmed, Porto Alegre, Brazil). For the data analysis, the highest value is recorded if it does not exceed the second highest value by 10% [27].

Endothelial function

Noninvasive measurements of endothelial function are obtained by flow-mediated dilation of the brachial artery using two-dimensional ultrasonography. Its measurement is performed in accordance with published guidelines [28] always by the same trained operator (MALS). Briefly, the examination starts after a 15-minute rest in a temperature-controlled room with the patient supine and the arms in a comfortable position. Any vasodilators are discontinued at least 4 hours before the examination if possible. The individuals are advised to refrain from exercising, drinking caffeine, and smoking for at least 4 hours before the examination.

Lean body mass

The arm muscle circumference is obtained from arm circumference and tricipital skinfold measurement using a tape measure and an adipometer, respectively [29].

Adherence

Adherence to an exercise program has been classified as meeting at least 80% of the recommended or prescribe exercise dose. Any participant who demonstrates a training protocol adherence of 80% or more than 36 sessions will be considered adherent. Participants will be classified as non-adherent or partially adherent if their adherence is less than 80% [30].

Sample size

Our sample size calculation was based on Feiereisen et al., who enrolled subjects with HF with reduced ejection fraction to assess the effect of strength in comparison with aerobic and combined aerobic-strength training on their peak VO_2 [31]. Considering a power of 80%, a significance level of 5% and an effect size of 0.2 for the peak VO_2, a total sample size of 32 subjects was estimated, including 16 in each study group. To account for a 20% estimated participant loss or refusal rate, we defined that 19 patients should be enrolled in each group, totalizing 38 subjects.

Recruitment

The patients are recruited from the outpatient HF clinic of Hospital de Clínicas de Porto Alegre. The recruitment period for the study is planned to range from October 2017 to July 2020. Eligible patients are informed of the study and invited to participate; those who accept are tested by a blinded assessor and randomly allocated to one of the study groups. A flow diagram of the patient recruitment process is shown in Figure 2.

Assignment of interventions and blinding

Group allocation was determined by eight blocks of 4 individuals (Software Rx64 version 3.1.1) in a 1:1 ratio generated by an external researcher. The investigator in charge of randomization does not participate in the other data collection stages. Allocation concealment is implemented through a central randomization routine conducted by investigators with access to the randomized list and the investigator charged with requesting the code to place subjects in the intervention group. In brief, the assigner contacted the external researcher to request whenever one or more subjects should enter an intervention arm. Thereafter, the external researcher will consult the code in consecutive order and uncover the code relative to the requested subject(s). Such requests will be documented and archived for further accountability. To ensure intervention blinding, communication with participants is not performed by the investigators involved in the outcome assessments.

Due to the nature of the interventions, the researcher conducting the exercise sessions as well as participants are not blinded. To ensure assessor masking, the subjects are asked to omit their assigned group and not to talk about their interventions during the outcome evaluation sessions. In the case of unintentional unblinding for any reason, the involved researcher will notify the principal researcher. In such cases, participant ID, date, and unblinding circumstances will be documented for internal control.

Data collection

Standard operating procedure documents are available for each assessment. The outcome assessors were trained and the handling of a standard operating procedure short version is mandatory during each data collection period. All variables will be assessed at baseline (prior to randomization) and at study completion.

Statistical analysis

The characterization of the sample will be performed by descriptive statistical analysis using measures of central tendency (mean and median) and variability (standard deviation and interquartile range). The normality of the data will be tested by the Shapiro-Wilk test. Intra- and inter-group analyses will be performed before and after the total 12-week intervention period. For both analyses the generalized estimation equations (GEE) will be used. Correlations between peak VO_2 and study variables – quality of life, functionality, muscle strength, endothelial function, and lean body mass – will be examined by Pearson or Spearman coefficients as appropriate.

In all tests, a significance level of $p < 0.05$ will be adopted. All data will be analyzed using SPSS Statistics for Windows version 20.0 (IBM Corp., Armonk, NY, USA) by the intention-to-treat and protocol methods.

Dropouts (essentially, participants who withdraw consent for continued follow-up) or missing data will be included in the analysis by modern imputation methods.

Monitoring

Data monitoring

The study does not have a data monitoring committee. We reason that this committee would not be mandatory due to the characteristics of the interventions and outcomes despite the trial's high overall quality.

Harms

The study will monitor for the following physical training-related adverse effects during the intervention period: shortness of breath, fatigue, and muscular pain. The

researcher responsible for the intervention will identify possible solutions for any adverse effects.

Auditing

If necessary, auditing will be conducted by the Hospital de Clínicas de Porto Alegre using defined protocols implemented by an independent monitoring team adjunct to the research board structure.

DISCUSSION

Thirty-five percent of HF patients die within 5 years after diagnosis, and this syndrome remains the major cause of hospitalization for patients older than 65 years of age. Thus, its impact in the health care systems is high [32].

The present study is the first to evaluate the effect of functional training in HF patients. This modality emerged from the training of athletes and the rehabilitation of sports injuries and lower back pain [17]. It was mainly studied in elderly populations with a focus on reducing the fall risk and late-life disability [14, 15, 16].

Compared to a moderate-intensity walking program, a functional circuit training program performed at high intensity for 6 weeks by sedentary subjects significantly improved their maximum leg and shoulder strengths. The maximum cycling workload evaluated on a bicycle ergometer was also significantly higher in the functional training group, whereas maximal VO_2 and ventilatory threshold were not [33]. In fact, this study enrolled a healthy and young population (mean age, 25 ± 5 years old) constantly exercised at submaximal intensity. It is possible that functional training could lead to a more expressive improvement in cardiorespiratory parameters when performed by individuals with lower physical fitness and some degree of disability, such as those with HF.

Exercise intolerance is a hallmark symptom of HF and associated with increased disability and mortality [34]. The sedentary lifestyle adopted by individuals with HF leads to peak VO_2 reductions and poor quality of life [35]. Although VO_2 is an important prognostic predictor of HF, its increase is not related to improvement in left ventricular ejection fraction, and a recovery of central hemodynamic function does not translate to improved exercise performance [36]. On the other hand, VO_2 is significantly correlated with quadriceps muscle mass, mean arm circumference, and muscle area, suggesting that atrophy of the peripheral muscles contributes to exercise intolerance in patients with HF [37]. Skeletal muscle strength is strongly correlated with morbidity and mortality of patients with HF and an independent predictor of peak VO_2 [9].

Different combinations of aerobic (continuous and interval), strength/resistance, and inspiratory exercise training have been proposed to patients with HF [38]. Laoutaris et al. [37] randomized 27 patients to a 12-week aerobic or a combined aerobic, resistance, and inspiratory muscle training program. The combined protocol demonstrated a significantly greater increase in quadriceps strength and resistance than aerobic training alone. However, the increase in peak VO_2 and MIP were similar in both groups. Dall'Ago et al. [39] evaluated the effects of inspiratory muscle training in inspiratory muscle strength and functional capacity in patients with HF and inspiratory muscle weakness. After the 12-week training period, the patients in the intervention group demonstrated significantly improved functional capacity as evidenced by an increased 6-minute walk distance and peak VO_2 versus the placebo group. Quality of life was also significantly increased in the trained group. Maiorana et al. [40] randomized 36 untrained subjects with HF to 12 weeks of resistance training, aerobic training, or an untrained control group. Peak VO_2 increased after 12 weeks of aerobic training and 6 and 12 weeks of resistance training but decreased in controls at 12 weeks.

The diversity of training protocols makes it difficult to generalize the findings cited above and the question remains open: Is there a complete protocol for physical training for patients with HF?

It is important that we investigate the benefits of functional training that mimics the daily activities with a combination of resistance/strength muscle and aerobic exercise.

Abbreviations

ADL, activities of daily living; **HF,** heart failure; **HR,** heart rate; **LVEF,** left ventricular ejection fraction; **MIP,** maximal inspiratory pressure; **NYHA,** New York Heart Association; **VO_2,** oxygen consumption

Declarations

Ethics approval and consent to participate

The study procedures were approved by the research ethics board from the Hospital de Clínicas de Porto Alegre on August 8, 2017 (protocol No. 20170291). The informed consent document includes the objectives of the study, a description of the testing procedures, explanation about interventions and its randomized allocation nature, the potential risks and benefits involved in the study, information on anonymized data sharing, and liabilities of the researcher staff. Once a subject decides to participate, a signed and personally dated informed consent is obtained from the subject before any trial-related procedure. The investigator charged of providing study clarifications and seeking the participant's ethical consent must allow the subject sufficient time to decide whether or not to participate in the trial. A copy of the consent form is given to the participant.

Consent for publication

Not applicable.

Availability of data and materials

We support the reuse of scholarly data and intend that the data to be collected in this trial may contribute beyond our actions to the knowledge on exercise and non-pharmacological management of HF. First, we will provide in writing the final results of the research for each participant. Second, we have obtained ethical consent from participants as well as research ethics board approval to share deidentified data after trial completion through presentation in congresses and publications in journals.

Competing interests

All authors have no competing interests to disclose.

Access to data

All the investigators involved in the trial will have access to the full dataset.

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Such funding agency do not have any roles regarding the design of the study, data collection, analysis and interpretation of data, or in writing the manuscript.

Authors' contributions

DMN and BDS were responsible for the study's rationale and generated the operating hypothesis for the study. DMN, PMB, ADS, MALS, LAG, NOC and BDS made major contributions for the protocol manuscript. DMN, KCM, PMB, ADS, MALS, LAG, NC and BDS contributed in intellectual, organizational and logistic frameworks for data collection, interventions' rationale and implementation, allocation concealment, data assessors blinding and other important aspects of study workflow, together with critically reviewing the manuscript.

All authors have read and approved the manuscript.

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Figure legends

Figure 1: Examples of functional exercises.

Legend: 1, run on trampoline; 2 (a, b), Swiss ball wall squat; 3, overhead press with dumbbells; 4 (a, b), plank and variation; 5, squat on rigid balance board; 6 (a, b), oblique twist with elastic band; 7, agility on ladder drills; 8 (a, b), reverse plank.

Figure 2: Proposed trial design.

628 **Table 2.** Functional training protocol: exercises and periodization model

Phase 1	Run on trampoline	- 3 sets of 40 sec
-4 weeks-	Sit to stand (body weight)	- 2 sets of 30 sec
	Biceps curls with elastic band	- 2 sets of 10-12 rep
	Suicide	- 2 sets of 30 sec
	Sumo squat (with 4-kg kettlebell)	- 2 sets of 30 sec
	Standing band row	- 2 sets of 10-12 rep
	Low step up (10-cm height)	- 2 sets of 40 sec
	Lateral band walk	- 2 sets of 30 sec
	Basic crunch	- 2 sets of 10-20 sec
	Hip adductor ball squeeze	- 2 sets of 30 sec
	Frontal plank	- 2 sets of 15-20 rep
	Run on trampoline	- 3 sets of 40 sec
Phase 2	Run on trampoline	- 3 sets of 50 sec
-4 weeks-	Squat on rigid balance board	- 1 set of 30 sec for each side
	Oblique twist with elastic band	- 1 set of 10-12 rep for each side
	Side to side run with cones	- 1 to 2 sets of 30 sec
	Kettlebell high pull (4 kg)	- 2 sets of 10-12 rep
	Lunges (body weight)	- 1 to 2 sets of 30 sec for each leg
	Low step up (10-cm height)	- 2 sets of 50 sec
	Basic crunch	- 2 sets of 15-20 rep
	Reverse crunch	- 1 to 2 sets of 15-20 rep
	Swiss ball hip raise	- 1 set of 10 rep
	Frontal plank	- 1 to 2 sets of 10-20 sec

	Lateral plank	- 1 set of 10-20 sec
	Run on trampoline	- 3 sets of 50 sec
Phase 3	Run on trampoline	- 3 sets of 60 sec
-4 weeks-	Swiss ball wall squat	- 2 sets of 30 sec
	Triceps bench dips	- 2 sets of 10-12 rep
	Step up (20-cm height)	- 1 set of 30 sec for each leg
	Agility on ladder drills	- 1 to 2 sets of 30 sec
	Dumbbell shoulder press Swiss ball (2 kg)	- 2 sets of 10-12 rep
	Walking lunge (body weight)	- 1 to 2 sets of 30 sec
	Basic crunch	- 2 sets of 15-20 rep
	Reverse crunch	- 1 to 2 sets of 15-20 rep
	Hamstring curl with a Swiss ball	- 2 sets of 10-12 rep
	Reverse plank with leg lift	- 4 sets of 3 sec for each leg
	Plank with leg lift	- 1 set of 10 sec for each leg
	Run on trampoline	- 3 sets of 60 sec

629 Sec, second; Rep, repetition

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Figure 1

Figure 2