Dissertação

UMA SESSÃO ISOLADA DE TREINAMENTO INTERVALADO DE ALTA INTENSIDADE PROMOVE AUMENTO SUBAGUDO NO DIÂMETRO DA ARTÉRIA BRAQUIAL E REDUÇÃO NA PRESSÃO ARTERIAL EM PACIENTES COM INSUFICIÊNCIA CARDÍACA COM FRAÇÃO DE EJEÇÃO PRESERVADA

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Dissertação submetida como requisito para obtenção do grau de Mestre ao Programa de Pós-Graduação em Ciências da Saúde, Área de Concentração: Cardiologia e Ciências Cardiovasculares, da Universidade Federal do Rio Grande do Sul.

Porto Alegre, Dezembro 2015.

AGRADECIMENTOS

Ao Professor Dr. Ricardo Stein, pelo privilégio da sua orientação desde a Iniciação Científica, sobretudo pela confiança, companheirismo e constante incentivo.

À Rosane Maria Nery e Maurice Zanini por me apresentarem esse cenário fascinante da pesquisa científica e por todos os ensinamentos que seguem até hoje.

Ao Anderson Donelli da Silveira pela parceria na concepção e desenvolvimento deste trabalho.

Ao Márcio Garcia Menezes, Marco Aurélio Lumertz Saffi, Leila Denise Cardoso Ramos, Diogo Silva Piardi, Altair Ivory Heidemann Júnior, pela gentileza, disponibilidade e dedicação aos exames do estudo.

Aos amigos e colegas do Grupo de Pesquisa em Cardiologia do Exercício, Raquel Petry Buhler, Rafael Cechet de Oliveira e César Augusto da Silva, que tornaram essa caminhada ainda mais valiosa e gratificante.

Aos bolsistas de Iniciação Científica pelo auxílio nas coletas e oportunidade de ensinar e aprender. Agradeço à Francielle da Silva Santos pela sua participação do início ao fim deste trabalho e também àqueles que contribuíram em algum momento para que este fosse realizado.

Ao Serviço de Métodos não Invasivos, pelo espaço concedido às coletas. Assim como, à equipe de Técnicas e Enfermeiras que prontamente auxiliaram na preparação dos exames.

Ao Grupo de Pesquisa em Dor Osteomuscular e Reabilitação, pelas amizades e debates em que muito aprendi. Agradeço ao Professor Dr. Antonio Cardoso dos Santos pelo incentivo à pesquisa. À Daiane Dias Cabeleira que esteve presente nos estudos preparatórios para o mestrado e durante a realização do mesmo. Ao

Eduardo Lima Garcia por estar sempre disposto a compartilhar o seu conhecimento comigo.

Aos meus pais, Márcia Eliane Beust de Lima e Orlando Pires de Lima, pelo amor que sempre me fizeram sentir e colocar em tudo o que faço. Pelo apoio que me deram nas mais diversas situações, incentivo tão precioso e aconselhamentos fundamentais. Pela educação que me oportunizaram e principalmente pelos exemplos que são para mim.

Ao meu namorado, Gustavo Sepúlveda Silva, pelo companheirismo em todos os momentos. Por compartilhar de toda essa emoção e me motivar sempre a fazer o meu melhor.

Ao Programa de Pós Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares e à Universidade Federal do Rio Grande do Sul por esta oportunidade.

Agradeço especialmente a todos os pacientes que participaram espontaneamente desse trabalho, tornando-o factível e engrandecendo o nosso dia a dia.

"Conheça todas as teorias, domine todas as técnicas, mas ao tocar uma alma humana, seja apenas outra alma humana."

Carl Jung

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LISTA DE SIGLAS

BNP – peptídeo natriurético cerebral

DAB – diâmetro da artéria braquial

DAC – doença arterial coronária

DC – débito cardíaco

Dif a-v O_2 – diferença arteriovenosa de oxigênio

eNOS- enzima óxido nítrico sintase

EROs – espécies reativas de oxigênio

FC – frequência cardíaca

FEND – função endotelial

FVASC – função vascular

IC – insuficiência cardíaca

ICFEP – insuficiência cardíaca com fração de ejeção preservada

ICFER – insuficiência cardíaca com fração de ejeção reduzida

NO – óxido nítrico

NTG - nitroglicerina

NT-próBNP - fragmento N-Terminal do peptídeo natriurético tipo B

PA – pressão arterial

PAD – pressão arterial diastólica

PAS – pressão arterial sistólica

PAM – pressão arterial média

TCMI – treinamento contínuo de moderada intensidade

TIAI – treinamento intervalado de alta intensidade

VIE – vasodilatação independente do endotélio

VMF – vasodilatação mediada pelo fluxo

VO_2máx. – consumo máximo de oxigênio

INTRODUÇÃO

A insuficiência cardíaca (IC) é uma complexa síndrome clínica, de diversas etiologias e alta prevalência na população mundial (1,2). Pode ser definida como a incapacidade do miocárdio em prover o débito cardíaco necessário às demandas metabólicas do corpo, ou desempenhar essa tarefa à custa de altas pressões de enchimento devido a algum comprometimento estrutural ou funcional no enchimento ventricular ou na ejeção de sangue (2).

Estudos epidemiológicos demonstram que aproximadamente 50% dos indivíduos com IC apresentam fração de ejeção preservada (ICFEP), possuindo uma gama de fatores prognósticos que geralmente são semelhantes aos observados nos pacientes com fração de ejeção reduzida (ICFER) (3,4). Sinais e sintomas de IC, fração de ejeção preservada e disfunção diastólica com pressões de enchimento aumentadas do ventrículo esquerdo, são critérios diagnósticos para ICFEP (5).

O estado do endotélio vascular é importante para a progressão e patogênese da ICFEP (6–9). O novo paradigma para o desenvolvimento desta síndrome, identifica um estado pró-inflamatório sistêmico induzido por comorbidades como causa das alterações estruturais e funcionais do miocárdio (6). Ademais, a função endotelial (FEND) é atenuada em indivíduos com ICFEP (10,11), estando associada à classe funcional NYHA e sendo preditora independente de eventos cardiovasculares futuros (11,12). A hipertensão arterial sistêmica é a comorbidade mais prevalente e assim como a disfunção endotelial está envolvida no desenvolvimento da ICFEP. Além de contribuir para o excesso da pós-carga, está associada com aumento do estresse oxidativo e inflamação vascular. Estratégias de tratamento para esta síndrome devem visar tanto o controle da pressão arterial (PA) quanto a melhora da função endotelial (FEND) (6).

Mais recentemente foi aventado que a FEND possa contribuir para a intolerância ao exercício (13–17). Estudos recentes avaliaram o efeito do treinamento físico (adaptações crônicas) como estratégia não medicamentosa adjuvante no tratamento de pacientes com ICFEP. O treinamento físico aeróbico mostrou-se eficaz em melhorar a capacidade funcional, qualidade de vida e função diastólica na população estudada (18–21).

Entre as diversas modalidades de exercício, o treinamento intervalado de alta intensidade (TIAI) vem se mostrando eficaz no tratamento de diferentes cardiopatias, assim como no treinamento de indivíduos saudáveis. É uma alternativa segura (22) e prática em promover a saúde cardiovascular (23,24). Evidências sugerem superioridade do TIAI em comparação ao Treinamento Contínuo de Moderada Intensidade (TCMI) em melhorar a FEND em indivíduos com doenças cardiovasculares (24,25). No que tange a pressão arterial (PA), o TIAI mostrou-se tão eficaz quanto o TCMI em melhorar os níveis pressóricos de indivíduos com síndrome metabólica, sendo mais eficaz em melhorar a FEND e único em promover aumento na biodisponibilidade NO (26). Entretanto, resultados referentes à FEND e PA após treinamento em pacientes com ICFEP são limitados e inconclusivos. A saber, apenas dois estudos foram realizados: no primeiro, o treinamento contínuo não melhorou a FEND (27) e no segundo o TIAI também não melhorou a FEND, mas este foi um estudo piloto que contou com 9 pacientes e apenas um mês de intervenção (21).

Uma única sessão de exercício físico pode promover alterações subagudas na função vasomotora em pacientes com ICFER. Estes indivíduos, apesar da resposta vascular atenuada, apresentam melhora da FEND após uma sessão de exercício submáximo em cicloergômetro (28), assim como após exercício resistido (29). Neste cenário, uma sessão de TIAI mostrou-se capaz de aumentar o diâmetro da artéria braquial (DAB) e melhorar a FEND em indivíduos com fatores de risco (30) e também em sujeitos com doença cardiovascular (31,32). Além disso, uma sessão de TIAI foi eficaz em reduzir a pressão PA ambulatorial de pacientes hipertensos(33). Entretanto, há uma lacuna na literatura no que se refere às respostas subagudas na função vascular (FVASC) e PA após uma sessão de TIAI em pacientes com ICFEP.

REVISÃO DA LITERATURA

Treinamento físico na Insuficiência Cardíaca e Fração de Ejeção Preservada

A prevalência de ICFEP vem aumentando nos últimos anos. Por outro lado, as abordagens terapêuticas permanecem limitadas e baseadas no manejo de fatores de risco cardiovasculares. Além disso, métodos convencionais para o tratamento da ICFER são ineficazes em pacientes com ICFEP e a taxa de mortalidade permanece inalterada (2,4,9). Lançando-se mão de medidas não medicamentosas, o treinamento físico emerge como uma potencial estratégia a ser incluída no tratamento desses pacientes.

Alves e cols. (34) avaliaram o efeito do treinamento em cicloergômetro em pacientes com IC que foram classificados naqueles com fração de ejeção preservada (>55%), disfunção “borderline” (45%-54%) e nos que apresentam disfunção marcada (<45%). Os autores verificaram que o treinamento físico pode melhorar o curso da IC independentemente do grau de disfunção ventricular esquerda. Analisando especificamente pacientes com ICFEP, Edelmann e cols. (20) demonstraram que curto período de TCMI associado ao treinamento resistido é capaz de melhorar a capacidade funcional, função diastólica e qualidade de vida nesses indivíduos (20). Em contrapartida, no estudo de Smart e cols. (35), apesar do TCMI melhorar a capacidade funcional em pacientes com ICFEP, não houve melhora na função ventricular esquerda, tanto sistólica quanto diastólica, corroborando com estudo prévio de Kitzman (27) e cols. e formulando a hipótese de que a melhora da tolerância ao exercício também possa estar associada a adaptações musculares e vasculares.

Estudos recentes demonstram que além das alterações hemodinâmicas centrais, componentes periféricos contribuem para intolerância ao exercício em pacientes com ICFEP (36,37). Limitações globais na reserva cardiovascular, como cronotropismo, inotropismo, lusotropismo e vasodilatação, culminam em acoplamento ventrículo-arterial, resposta deprimida do débito cardíaco (DC), além

da redução da tolerância ao exercício (14,15,36,38). De acordo com o princípio de Fick, a redução do consumo máximo de oxigênio (VO_2máx.) é resultante de qualquer redução do débito cardíaco, da diferença arteriovenosa de oxigênio (Dif a-v O_2) ou de ambos. Foi demonstrado que em pacientes com ICFEP a Dif a-v O_2 reduzida contribui para limitada capacidade funcional.

Em estudo conduzido por Haykowisky e cols. (39) , o aumento da Dif a-v O_2 de pico (estimada pela equação de Fick), foi o principal contribuinte para o aumento do VO_2máx. após treinamento físico em pacientes com ICFEP. Posteriormente, o mesmo grupo conduziu um ensaio clínico randomizado para testar a hipótese de que TCMI melhoraria a FEND e a rigidez arterial nesses pacientes e que esta melhora poderia estar relacionada ao aumento do VO_2máx. Entretanto, contrariando a hipótese inicial, a despeito da melhora do VO_2máx., não houve aumento na FEND nos indivíduos treinados (27). Cabe destacar que foram excluídos deste estudo pacientes com qualquer evidência de aterosclerose devido a sua relação com a disfunção endotelial. Em contrapartida, excluiu-se parte representativa da população de pacientes com ICFEP, pois tal comorbidade é altamente prevalente nesses sujeitos. Esses resultados sugerem que o incremento do VO_2máx. em pacientes com ICFEP após treinamento físico, possa estar associado a adaptações microvasculares e/ou musculoesqueléticas que, por sua vez, aumentam a difusão do transporte de oxigênio e/ou sua utilização nos músculos ativos.

O estudo referido é o primeiro e único que avaliou o efeito do TCMI na FEND de indivíduos com ICFEP. Sendo assim, não podemos descartar o possível efeito do treinamento físico na FEND em uma população mais ampla desses pacientes. Ainda, é possível que TIAI seja mais eficaz em promover adaptações cardiovasculares nessa mesma população.

Treinamento Intervalado de Alta Intensidade: função endotelial e pressão arterial

A intensidade do treinamento está diretamente associada à magnitude das adaptações cardiovasculares(40). Contudo, para uma otimizada e segura prescrição do exercício físico em programas de reabilitação cardíaca, deve-se considerar a duração, intensidade e os períodos de descanso em cada sessão (23).

O TIAI alterna períodos mais intensos com momentos de recuperação passiva ou ativa (intensidade variável), possibilitando que uma alta intensidade de exercício seja mantida por mais tempo e, consequentemente, gerando um estímulo maior para adaptações fisiológicas centrais e periféricas. A prescrição deve ser feita conforme o protocolo de escolha e preferencialmente a partir de dados obtidos no teste cardiopulmonar de exercício (TCPE). Posicionamento conjunto da *European Association for Cardiovascular Prevention and Rehabilitation, American Association of Cardiovascular and Pulmonary Rehabilitation e Canadian Association of Cardiac Rehabilitation* apresenta o protocolo mais estudado e que se mostra superior ao TCMI em promover o incremento do VO_2máx., além da melhora no controle de fatores de risco em indivíduos com doenças cardiovasculares (23,41).

Recente metanálise comparou o efeito do TIAI ao TCMI na FEND avaliada pela vasodilatação mediada pelo fluxo (VMF) na artéria braquial. Nos estudos analisados foram incluídos 182 participantes com IC, doença arterial coronária (DAC), hipertensão arterial sistêmica, obesidade, diabetes melito, além de outras comorbidades. Como resultado, o TIAI foi superior ao TCMI em promover incremento na FEND. Este resultado sugere que o mesmo possa acontecer em indivíduos com ICFEP, devido às características da amostra analisada (25). Neste contexto, existem diversas possibilidades de prescrição de TIAI. Estudos que utilizaram o mesmo protocolo referido acima observaram que este foi eficaz em promover a melhora dos níveis pressóricos em pacientes hipertensos e com síndrome metabólica (26,42).

Wisloff e cols. randomizaram pacientes com ICFER de etiologia isquêmica para grupo TIAI, grupo TCMI e grupo controle (que recebeu aconselhamentos

padrões sobre atividade física). Ao final de doze semanas de seguimento, os pesquisadores verificaram que a intensidade do exercício foi fator importante em reverter o remodelamento do ventrículo esquerdo, aumentar o VO2máx. e melhorar a qualidade de vida, pois para esse e outros desfechos cardiovasculares o TIAI foi superior ao TCMI. Outro achado que merece destaque foi a melhora na FEND, a qual pareceu ter contribuído no incremento da capacidade funcional e se associou a melhora do estado antioxidante. Tal fato indica que esta estratégia de exercício foi capaz de produzir um nível mais baixo de espécies reativas de oxigénio (EROs) e uma maior produção de óxido nítrico (NO) (24).

Até o momento, apenas um estudo avaliou o efeito do TIAI em pacientes com ICFEP. Trata-se de um experimento piloto em que nove pacientes realizaram TIAI e seis TCMI. Os protocolos foram isocalóricos e ambos realizados três vezes por semana, durante um mês. Apenas o TIAI aumentou o VO_2máx. (pré: 19,2 ± 5,2mL.kg^{-1}.min^{-1}; pós: 21,0 ± 5,2mL.kg^{-1}.min^{-1}; p=0,04), reduziu o grau de disfunção diastólica (2,1 ± 0,3; 0,7 ±0,7; p=0,02) e a pressão arterial diastólica (pré: 85 ± 8mmHg; pós: 77 ± 8mmHg) Entretanto, assim como no grupo TCMI, um mês de TIAI não foi capaz de aumentar a FEND (21). O fato dos pacientes não apresentarem disfunção endotelial pode ter influenciado nas respostas da função vascular, assim como o curto período de intervenção e o número reduzido de sujeitos avaliados. Entretanto, também é possível que o treinamento físico não afete a função vasomotora de pacientes com ICFEP, contrastando com o observado na ICFER.

Exercício físico: respostas hemodinâmicas e vasculares

O endotélio vascular assume papel fundamental na modulação do tônus vascular. É composto por uma monocamada de células achatadas e sobrepostas que sintetizam e liberam, a partir de estímulos físicos, neurais e humorais, substâncias vasoativas que podem ser divididas em fatores relaxantes e constritores derivados do endotélio. Dentre estes, o NO ganha destaque, pois além de ser um potente vasodilatador, impede a proliferação das células musculares lisas, inibe

fatores pró-inflamatórios e a adesão celular, dificultando a formação de trombos e inflamação da parede vascular (43,44).

A tensão de cisalhamento é a força exercida pelo sangue que corre paralelamente ao eixo longitudinal dos vasos sanguíneos. Esse estímulo mecânico na membrana celular endotelial é ativador da enzima eNOS, responsável pela liberação do NO. Ela irá se difundir para o lúmen do vaso e para as células musculares lisas, resultando em vasodilatação dependente do endotélio (VDE), também conhecida como VMF (44,45). Sendo assim, a FEND reflete a mudança do diâmetro da artéria em reposta ao aumento do fluxo sanguíneo. Em humanos, geralmente é avaliada na artéria braquial ou femoral, onde a tensão cisalhamento é gerada a partir de hiperemia reativa induzida por um período prévio de oclusão no seguimento avaliado (46). Se a VMF estiver reduzida há disfunção endotelial, que é decorrente do desequilíbrio entre a síntese e remoção do NO (47). Intervenções que estimulem a síntese de NO contribuem para a integridade do endotélio e para homeostase vascular.

Em indivíduos hígidos, durante a realização de atividade física, o aumento do DC ocorre de forma proporcional ao incremento da intensidade. Isso permite o adequado suprimento de oxigênio para a musculatura ativa a partir do aumento do fluxo sanguíneo (48). O aumento da tensão de cisalhamento na parede vascular que ocorre durante a realização do exercício físico promove vasodilatação, da mesma forma que acontece a partir da hiperemia reativa gerada pela oclusão vascular. Pacientes com ICFEP apresentam reserva vasodilatadora atenuada. Durante exercício máximo em cicloergômetro, os pacientes com essa síndrome apresentaram atenuação na redução da resistência vascular sistêmica e no aumento do fluxo sanguíneo periférico em relação a sujeitos hipertensos e controles (14).

Alterações fisiológicas agudas que acontecem de forma imediata ao exercício antecedem os efeitos subagudos do mesmo, que são verificadas após a realização do esforço (49,50). Um bom exemplo disto é o comportamento da PA. Durante o exercício físico há aumento da PA sistólica (PAS) que é proporcional à intensidade do esforço, enquanto a PA diastólica (PAD) permanece igual ou apresenta um pequeno aumento (até 10mmHg). Logo após a realização do esforço a PA reduz a níveis inferiores aos mensurados em repouso, o que é reconhecido como efeito

hipotensor do exercício. No que se refere à FEND e às adaptações em longo prazo, repetidos episódios de aumento do fluxo sanguíneo e, por conseguinte, aumento na tensão de cisalhamento pode ser o mecanismo fundamental para as adaptações crônicas na função vascular resultantes do treinamento físico (51).

Foi demonstrado que após realização de exercício, indivíduos saudáveis apresentam FEND melhorada, a qual pode permanecer horas após a sessão de treinamento (52). Entretanto, pacientes com IC apresentam hemodinâmica cardiovascular prejudicada. Sullivan e cols. (53) verificaram que pacientes com ICFER, ao se exercitarem em cicloergômetro, apresentaram atenuação no aumento do fluxo sanguíneo e na redução da resistência vascular periférica nos membros ativos. Posteriormente, Umpierre e cols. (28) avaliaram as respostas subagudas ao exercício também neste tipo de paciente e constataram que apesar da resposta atenuada em comparação aos indivíduos saudáveis, houve aumento no fluxo sanguíneo e redução na resistência vascular no membro não exercitado após uma sessão de exercício no cicloergômetro. Achado que merece destaque foi o aumento da VMF no membro não exercitado, demonstrando que alterações na FEND sistêmica podem ocorrer após uma única sessão de exercício em pacientes com ICFER.

Conclusões sobre o efeito subagudo do exercício na FEND ainda são inconsistentes, o que pode ser atribuído ao fato dos estudos distinguirem-se em relação aos estímulos utilizados (tipo, intensidade e duração do exercício), a população estudada (sedentários/treinados, saudáveis/doentes) e principalmente a metodologia aplicada durante as avaliações (tempo de aferição e mudança no diâmetro basal da artéria após o esforço) (51). O que está bem definido na literatura é a relação entre a intensidade do esforço e a tensão de cisalhamento na parede vascular, que por sua vez é um importante estímulo mecânico para as adaptações vasculares. A partir disso, estudos foram delineados para verificar o efeito subagudo da alta intensidade sobre a FEND baseado no exercício intervalado. Hallmark e cols. (30) verificaram que tanto uma sessão de TIAI quanto de TCMI foram eficazes em promover a melhora da FEND em pacientes obesos, enquanto que em indivíduos eutróficos, apenas a sessão de TIAI aumentou a VMF uma hora após a realização do exercício. Currie e cols. obtiveram achados semelhantes ao observarem que em

pacientes com DAC houve aumento da FEND após a realização de ambos protocolos(31).

JUSTIFICATIVA E OBJETIVO

Embora os efeitos do treinamento aeróbico sobre a FVASC de pacientes com ICFER têm sido bem estudados, menos se sabe sobre o que ocorre de forma subaguda após uma única sessão de TIAI. As evidências disponíveis demonstram que uma única sessão de exercício aeróbico pode promover melhora subaguda na FEND e na PA. Já, em pacientes com ICFEP, as respostas subagudas a uma única sessão de TIAI sobre a FVASC e a PA não são conhecidas. Sendo assim, o objetivo deste experimento foi o de avaliar o efeito subagudo de uma sessão isolada de TIAI na FEND, DAB e PA em pacientes com ICFEP.

HIPÓTESES: HO E H1

H0: Trinta minutos após uma sessão isolada de TIAI, pacientes com ICFEP não apresentam aumento no diâmetro da artéria braquial, melhora na FEND e redução na PA.

H1: Trinta minutos após uma sessão isolada de TIAI, pacientes com ICFEP apresentam aumento no diâmetro da artéria braquial, melhora na FEND e redução na PA.

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Article

An isolated high intensity interval training session promotes subacute increase in brachial artery diameter and reduction in blood pressure in patients with heart failure and preserved ejection fraction

Abstract

Introduction: In patients with heart failure and preserved ejection fraction (HFpEF), subacute responses to a high intensity interval training session (HIIT) on vascular function (VF) and blood pressure (BP) are not known.

Objective: To evaluate the subacute effect of a HIIT isolated session on the VF and BP in HFpEF.

Methods: Sixteen patients with HFpEF underwent a session of 36 minutes of HIIT on a treadmill alternating four minutes of high intensity with three minutes of active recovery. The diameter of the brachial artery (DBA), endothelial function (EF), and the BP were assessed immediately before and 30 minutes after HIIT.

Results: There was an increase in DBA (pre: 3.96 ± 0,57mm; post: 4.33 ± 0,69mm; p = 0.004) and reduced systolic BP (pre: 138 ± 31mmHg; post: 125 ± 19mmHg; p = 0.006). Both, the diastolic BP (pre: 81 ± 11mmHg; post: 77 ± 8mmHg) and the flow-mediated vasodilation (pre: 5.91 ± 5.20%; post: 3.55 ± 6.59%; p = 0.162), presented no significant change. There were no adverse events throughout the experiment.

Conclusion: After 30 minutes of a single HIIT session, DBA increases, BP reduces, but no significant change occurs in EF in patients with HFpEF. These findings point in the direction that HIIT can be effective in this setting.

Key words: Physical exercise; endothelial function; hypotension; heart failure with normal ejection fraction.

Introduction

Epidemiological studies show that approximately 50% of patients with heart failure (HF) have preserved ejection fraction (HFpEF) (1- 4) having prognosis similar to that observed in subjects with reduced ejection fraction (HFrEF). Moreover, with aging of the population, the prevalence of HFpEF has increased in recent years (1,5).Unfortunately, the drugs successfully used for the treatment of HFrEF are much less effective in patients with HFpEF. Therefore, therapeutic approaches in this clinical syndrome are still limited, being predominantly based on symptom management, as well as in controlling cardiovascular risk factors (4, 6, 7).

Hypertension is the most prevalent comorbidity in this syndrome (8). Besides contributing to an increased afterload, it is associated with oxidative stress and vascular inflammation, consequently stimulating endothelial dysfunction (9, 10). In turn, attenuated endothelial function (EF) in individuals with HFpEF (11 - 13) contributes to exercise intolerance (12, 14, 15), is associated with both NYHA functional class (13) and pulmonary hypertension (16), and is an independent predictor of future cardiovascular events (13, 17, 18).

In such a complex setting, any action that may have beneficial impact is welcome. When resorting to non-drug measures, physical training emerges as a potential strategy to be included in the treatment of these patients (19.20). In this regard, high intensity interval training (HIIT) has emerged as an exercise technique capable of impacting positively on some cardiovascular outcomes being as, or more, effective than moderate intensity continuous training (MICT) (21), including, in some patients with HF (22).

In other clinical settings, previous studies demonstrate that an isolated session of HIIT promoted subacute changes in vascular function (VF) and blood pressure (BP). After a HIIT session, patients with coronary artery disease (CAD) (23, 24) and obese (25) subjects showed an increase in diameter of the brachial artery (DBA) and improvement in endothelial function (EF). Likewise, hypertensive individuals presented lower BP after a HIIT session (26). In patients with HFREF, a single bout of exercise promotes subacute changes in vasomotor function, improving EF after a submaximal cycling (27) and resistance exercise (28). However, the subacute effect

of a single bout of exercise, mainly HIIT, on VF and BP pressure in HFpEF is still unknown.

It is possible that HIIT can have a positive impact on the VF of patients with HFpEF and might effectively assist in the control of BP, a potential strategy to be included in the treatment of this syndrome. Thus, the objective of this experiment was to evaluate DBA, EF, and BP 30 minutes after a single session of TIAI in patients with HFpEF.

Methods

Quasi-experimental study conducted between June 2014 and November 2015 in a tertiary hospital in southern Brazil. It included 22 patients with signs and symptoms of heart failure, diastolic dysfunction of the left ventricle, and ejection fraction >50% sequentially allocated in outpatient cardiology clinic of that institution. Eligibility criteria were: a) age between 40 and 75 years; b) NYHA functional class between I and III; c) to be clinically stable and under optimal drug therapy in the last 3 months. Patients with severe lung disease, valve disease, peripheral arterial disease, autonomic neuropathy, unstable angina, and complex arrhythmias induced by stress were excluded. Likewise, patients with implantable cardiac electronic devices and those with cognitive and/or limiting musculoskeletal conditions that prevented performance of any part of the experiment were excluded.

The study was approved by the local ethics committee under number 130471 and all participants signed the informed consent prior to participation. HFpEF was characterized according to the criteria of the European Society of Cardiology (29), and to confirm the diagnosis, the patients underwent Doppler echocardiography with color flow mapping, as well as blood sampling for analysis of N-Terminal Fragment of Natriuretic Peptide Type B (NT- pro-BNP) or Brain Natriuretic Peptide (BNP). After confirming the diagnosis of HFpEF, Cardiopulmonary Exercise Test (CPET) was performed to assess the clinical condition of the subject and obtain the necessary

data aiming at a proper exercise prescription protocol to be used. On another day, flow-mediated vasodilation (FMV) and endothelium-independent vasodilation (EIV) were measured through brachial artery Doppler ultrasonography, along with pre and post HIIT BP readings.

HIIT Protocol

The exercise was performed on a treadmill (General Electric T-2100, USA), having started with a warm-up of 8 minutes at an intensity of 60-70% HR max. Then four periods were performed, lasting 4 minutes each of exercise at 85-95% HR max, which corresponds to 15-17 on the Borg scale (21), alternate with 3 minutes at 60-70% HR max, corresponding to 11-13 on the Borg scale. The workout ended with 3 minutes of cool-down at moderate intensity (30). The HR band (target zone) stipulated for each block was determined from the HR max. obtained in the CPET of each individual, except for one patient with atrial fibrillation, for whom we used ventilatory thresholds 1 and 2 (anaerobic threshold and respiratory compensation point). It were recorded the HR through 12-lead electrocardiographic monitoring (Nihon Kohden Corporation, Japan), perceived exertion level referred on Borg scale, speed and incline used in each exercise period.

Cardiopulmonary Exercise Test

All tests were performed in the morning, with room temperature between 22º and 26°C and relative humidity around 60%. The maximum functional capacity was measured by CPET performed on a treadmill (General Electric T-2100, GE Healthcare, USA) associated with an analyzer of exhaled gases. The test was always performed by the same cardiologist, who has qualification for this exam given by the Department of Ergometry, Exercise, and Cardiopulmonary Rehabilitation of the Brazilian Society of Cardiology (Departamento de Ergometria, Exercício e Reabilitação Cardiopulmonar da Sociedade Brasileira de Cardiologia, DERC-SBC).

Ramp protocol was used, individualized according to the patient's physical condition, in order to achieve fatigue in a time of 8 to 12 minutes. In the pre-test period, the assessed individual walked between 2 to 4 minutes to adapt to the treadmill. Continuous 12-lead electrocardiographic (Nihon Kohden Corporation,

Japan) monitoring was performed by modification proposed by Mason-Likar (31), which was used to determine the HR peak. Measurement of BP was performed with sphygmomanometer (PA 2001, P.A. MED, Brazil) every two minutes during the test and every minute during recovery (until the eighth minute after the test). Oxygen consumption (VO_2), carbon dioxide production (VCO_2), minute ventilation (V_E) and respiratory quotient (R) were measured cycle to respiratory cycle using a commercial system (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany), previously validated. Peak VO_2 was considered the highest consumption achieved in the last seconds of the exercise.

The ventilatory reserve (VR_E) was obtained from the ratio between the maximum ventilatory volume (V_EMAX/MVV), expressed in %, and MVV calculated through the product between FEV_1 x 37.5. The slope of the V_E/VCO_2 was obtained through a regression using the whole exercise period. The tests were considered maximal when the R is equal to, or greater, than 1.10.

Brachial Doppler Ultrasound

Non-invasive measurements of EF were made by FMV in the brachial artery with two-dimensional ultrasound machine (Philips Ultrasound, USA). Patients were instructed not to perform any type of exercise, not smoke, nor consume caffeine and alcohol for 24 hours before evaluation. Evaluation started after 15 minutes resting in a room with temperature controlled between 18º and 22ºC, and the patient in a supine position with the left arm positioned comfortably.

Image of the brachial artery was obtained above the antecubital fossa in a longitudinal plane and the diameter was measured from the anterior and posterior intimal layer of the artery. After registration of basal diameter, a sphygmomanometer was inflated on the left forearm and remained so for 5 minutes. After disinflation of the sphygmomanometer a new image was recorded synchronized with the R wave of the electrocardiogram for measuring the artery diameter during reactive hyperemia, enabling the measurement of FMV.

After 15 minutes (for normalization), the basal diameter was measured again. Further, a sprayed dose (0.4mg) of nitroglycerin (NTG) was sublingually administered

and 5 minutes after the image was registered again to measure the brachial artery diameter to evaluate the EIV.

The FMV and EIV were expressed as the percentage change of artery diameter and defined as [(post-hyperemia or post-NTG diameter - pre-occlusion or pre-NTG diameter) / pre-occlusion or pre-NTG diameter] x 100, where [(post-hyperemia or post-NTG diameter - pre-occlusion or pre-NTG diameter) is the absolute difference in artery diameter (32, 33).

Transthoracic echocardiogram

Patients were examined at rest and in left lateral decubitus. A transducer was placed on the chest of the subject evaluated by which signals are transmitted and converted into moving images to the ultrasound system (Philips Ultrasound, USA). We evaluated the parameters suggested by the European Society of Cardiology (29) for the diagnosis of HFpEF and the procedure was carried out according to the current guidelines of the American Society of Echocardiography (34).

N-Terminal Fragment of Natriuretic Peptide Type B (NT-proBNP) and Brain Natriuretic Peptide (BNP)

Blood samples were collected after 15 minutes of rest. Analyses were performed by the method of electrochemiluminescence and analyzed by Roche Kit version proBNP II (04842464190 code) in equipment Cobas 8000 modular analyzer series (Roche Diagnostics, USA).

Blood pressure

BP was always checked by the same examiner through digital device (G-Tech MA100, Shenzen, China) in four distinct stages: 1) Pre-assessment of endothelial function (after 15 minutes of seated rest); 2) immediately before HIIT session; 3) 5 minutes after HIIT session; 4) 30 minutes after HIIT session.

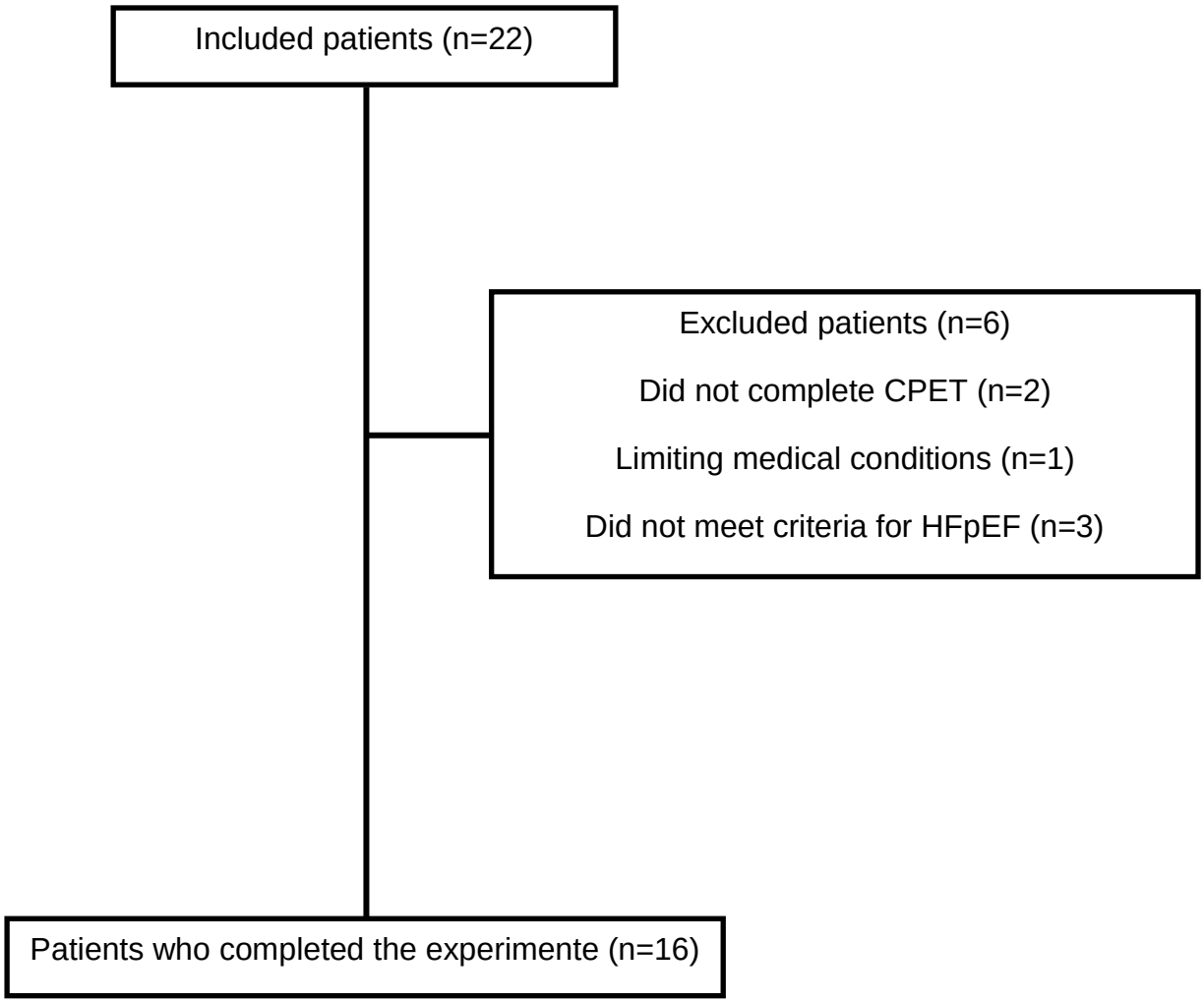
Statistical Analysis

Categorical variables are presented as absolute frequencies and percentages. Continuous variables with normal distribution are presented as mean and standard deviation, and those without normal distribution presented as median and interquartile range (IQR). After meeting the assumptions of normality, Student's T test for paired samples was used for comparing mean pre and post-exercise. If the assumptions of normality were missed, the Wilcoxon test for paired samples was used as a nonparametric test option for comparison of median pre and post-exercise. Generalized estimating equations (GEE) were used to compare mean BP and HR. The collected data were analyzed using the Statistical Package For Social Sciences (SPSS version 20.0). In all analyzes a value $P<0.05$ was considered significant. For a 5% significance level, a difference detection power of 80% and a difference considered to be at least 8% (absolute value) of FMV, Wisløff et al. study (22) was used, with a calculation sample size of 15 individuals.

Results

A sample of 22 patients were allocated to the study. Among these, three individuals who did not meet the diagnostic criteria for HFpEF, two who did not complete CPET and one that presented limiting medical conditions were excluded. The others continued until the end of the experiment (Figure 1). Table 1 shows the demographic, anthropometric, and clinical variables. Analysis by NT-pro-BNP and BNP was performed on a smaller group of patients (n=12), which was possible only after release of the budget for collection of these biomarkers.

Figure 1: Flow chart of the study patients.



CPET: Cardiopulmonary Exercise Test; HFpEF: Heart Failure and Preserved Ejection Fraction.

Table 1: Characteristics of the Sample.

Variables	n=16
Male	7 (44%)
Age (years)	59 ± 7
Weight (kg)	87 ± 28
Height (cm)	159 ± 10
Body mass index (kg/m^2)	34 ± 7
Waist circumference (cm)	110 ± 17
Smoking	
Active Smoker	2 (12%)
Former Smoker	7 (44%)
NYHA Functional Classification	
II	12 (75%)
III	4 (25%)
BNP and NT-pro-BNP (pg/ml)	
BNP > 200 or NT-pro-BNP > 220	3 (25%)
BNP < 200 or NT-pro-BNP < 220	9 (75%)

Data are reported as mean ± standard deviation and absolute frequency and percentage. NYHA: New York Heart Association; BNP: B-Type Natriuretic Peptide; (NT-pro-BNP): N-Terminal Fragment Type Natriuretic Peptide B; Former Smoker (+ than 1 year without smoking).

In Table 2 clinical variables related to comorbidities and medications used by individuals studied are added.

Table 2: Clinical Characteristics.

Variables	n=16
Comorbidities	
Hypertension	16 (100%)
Diabetes	7 (44%)
Rheumatic disease (Gout)	2 (12%)
Atrial fibrillation	1 (6%)
CRF	4 (25%)
AMI	2 (12%)
Stroke	3 (19%)
Medicines	
ACEI/ARA	16 (100%)
Beta Blockers	13 (81%)
Diuretics	13 (81%)
Blockers Ca^{++} channel	11 (69%)
Statins	10 (62%)
Antiplatelets	9 (56%)
Vasodilators	7 (44%)
Hypoglycemics	7 (44%)
Spironolactone	3 (19%)
Nitrates	2 (12%)
Anticoagulants	1 (6%)

Data are reported as absolute and percentage frequency. CRF: chronic renal failure; AMI: acute myocardial infarction; ACEI: the angiotensin-converting enzyme inhibitors; ARA: angiotensin receptors.

The structural and functional echocardiographic variables are shown in Table 3.

Table 3: Echocardiographic Variables

Variables	n=16
LVEF (%)	68 ± 5
E/e’	13 ± 4
LA (cm)	4.22 ± 0.41
ESV (ml)	37.9 ± 9.10
EDV (ml)	124.41 ± 23.24
EDVI (ml/m^2)	67.09 ± 6.35
ST (cm)	1.15 ± 0.17
PWT (cm)	1.10 ± 0.19
LVM (g)	244.35 ± 58
LMVI (g/m^2)	146.2 ± 35.84
LAVI (ml/m^2)	38.76 ± 6.96

Data with normal distribution are shown as mean ± standard deviation. Data without normal distribution are described as median ± interquartile range. LVEF: left ventricular ejection fraction; E/e’: early filling ratio of the flux wave of the left ventricle and the wave myocardial early offset; LA: left atrium; LAV: left atrial volume indexed to body surface; ESV: left ventricular end-systolic volume; EDV: left ventricular end-diastolic volume; ESVI: corporal left ventricular end-diastolic volume indexed to body surface; ST: septum thickness; PWT: posterior wall thickness; LVM: left ventricular mass; LVMI:left ventricular mass indexed by body surface; LAVI: left atrial volume indexed to body surface.

Table 4 exposes variables at CPET. We observed that patients showed reduced functional capacity and increase in the VE/VCO_2 slope. An R peak equal to 1.16 confirms maximality of the tests.

Table 4: Variables obtained in cardiopulmonary exercise testing.

Variables	n=16
VO_2 peak ($mL.kg^{-1}min^{-1}$)	18.40 ± 3.16
HR max. (bpm)	125 ± 23
VE/VCO_2 slope	33 ± 6
PET CO_2 rest (mmHg)	33 ± 3
Pulse O_2	11.36 ± 4.45
R peak	1.16 ± 0.13

Data with normal distribution are shown as mean ± standard deviation. Data without normal distribution are described as median ± interquartile range. VO_2 peak: peak oxygen consumption; HR max.: maximum heart rate; VE/VCO_2 slope: incline of the ventilatory equivalent of carbon dioxide; PET CO_2 rest: expired pressure of carbon dioxide; O_2 pulse: oxygen pulse; R peak; respiratory quotient.

All 16 patients completed the study protocol. The minimum and maximum speed and incline for moderate and intense blocks are described in Table 5, as well as the HR and subjective effort according to the original scale of Borg (6 to 20). The load (speed and incline) used in HIIT protocol was similar to that recorded in the CPET for each target area.

Table 5: Exercise protocol variables

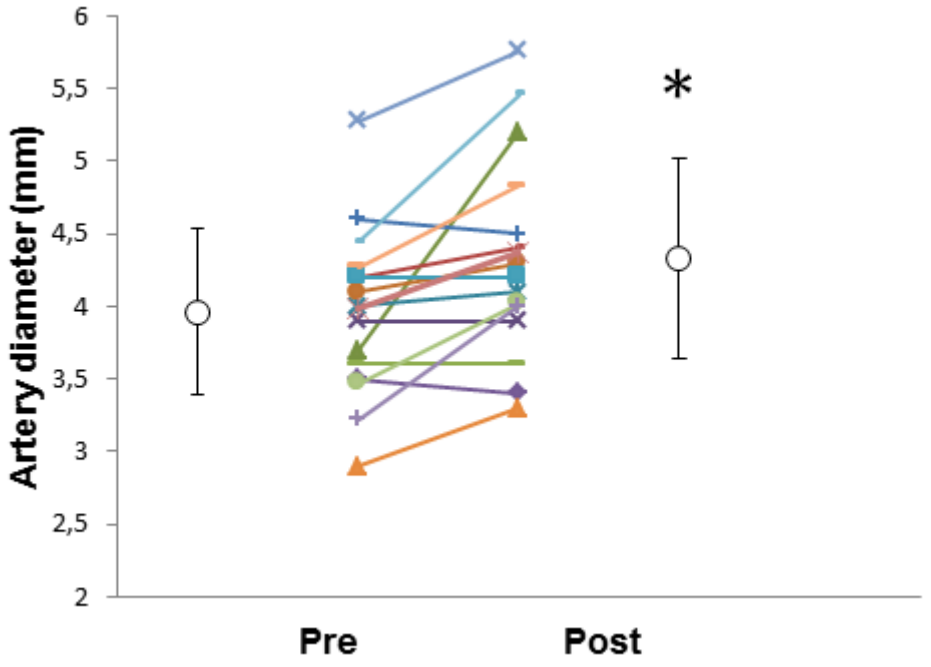
Variables	Moderate intensity	High Intensity
HR (bpm)	98 ± 19	113 ± 24
BORG	11 ± 2	14 ± 2
Speed (km/h)	2.5 – 3.8	3.8 – 6.3
Incline (%)	0 – 3	3 – 10

Data are reported as mean ± standard deviation and minimum and maximum limit. HR: heart rate; BORG: scale of perceived exertion.

Vascular Function

A single session of HIIT promoted subacute increase in the DAB, as shown in Figure 2. There was a significant difference of 0.37 mm in the artery (pre-exercise: 3.96 ± 0,57mm; post-exercise: 4.33 ± 0,69mm, p = 0.004).

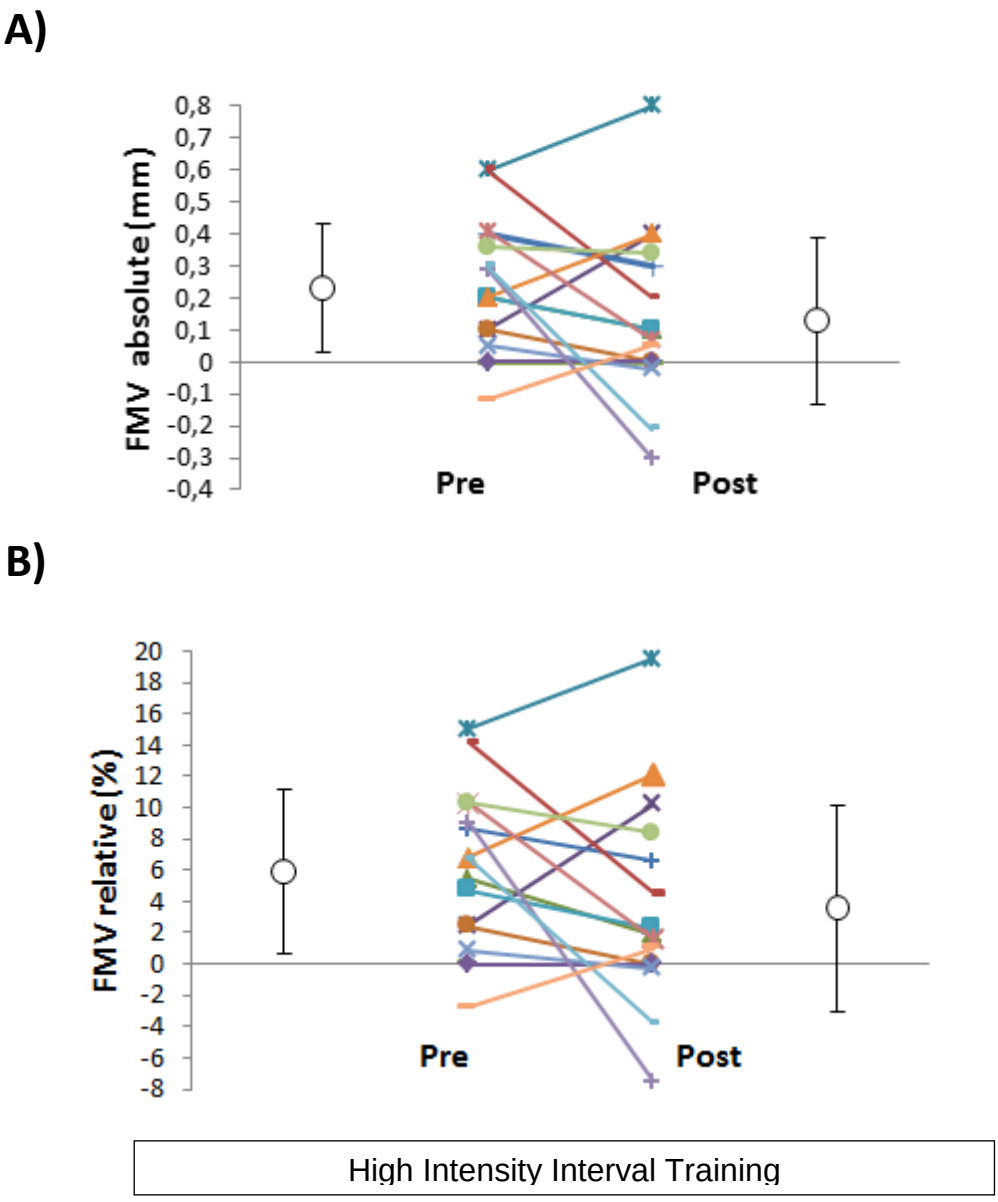
Figure 2: Brachial artery diameter pre and post High Intensity Interval Training Session



* p=0.004

There was no difference in the FMV from the reactive hyperemia stimulus, which is expressed by the absolute difference in the diameter of the artery and the percentage change in artery diameter (absolute FMV: pre: 0.23 ± 0.20mm; post: 0.13 ± 0.26mm; p = 0.177 and relative FMV: pre: 5.91 ± 5.20%; post: 3.55 ± 6.59%; p = 0.162); Figures 3.

Figure 3. Flow-mediated vasodilatation



FMV: Flow-mediated vasodilatation; A) Absolute difference in artery diameter; B) Percent variation in artery diameter.

There was no difference in the diameter of the artery and vasodilation in response to NTG (EIV) after a single session of exercise (Table 6).

Table 6: Diameter of the brachial artery and vascular responses to nitroglycerin before and 30 minutes after a High Intensity Interval Training session.

Variables	Pre	Post	P
Diameter of artery pre-occlusion (mm)	3.96 ± 0.57	4.33 ± 0.69	0.004
Diameter of artery post-occlusion (mm)	4.19 ± 0.61	4.47 ± 0.66	0.016
Diameter of the artery pre-NTG (mm)	4.11 ± 0.65	4.16 ± 0.68	0.528
Diameter of the artery post-NTG (mm)	4.57 ± 0.65	4.52 ± 0.64	0.541
Absolute NTG (mm)	0.46 ± 0.17	0.35 ± 0.20	0.106
Relative NTG (%)	11.4 ± 4.4	9.0 ± 5.37	0.117

Data are reported as mean ± standard deviation. NTG: Nitroglycerin.

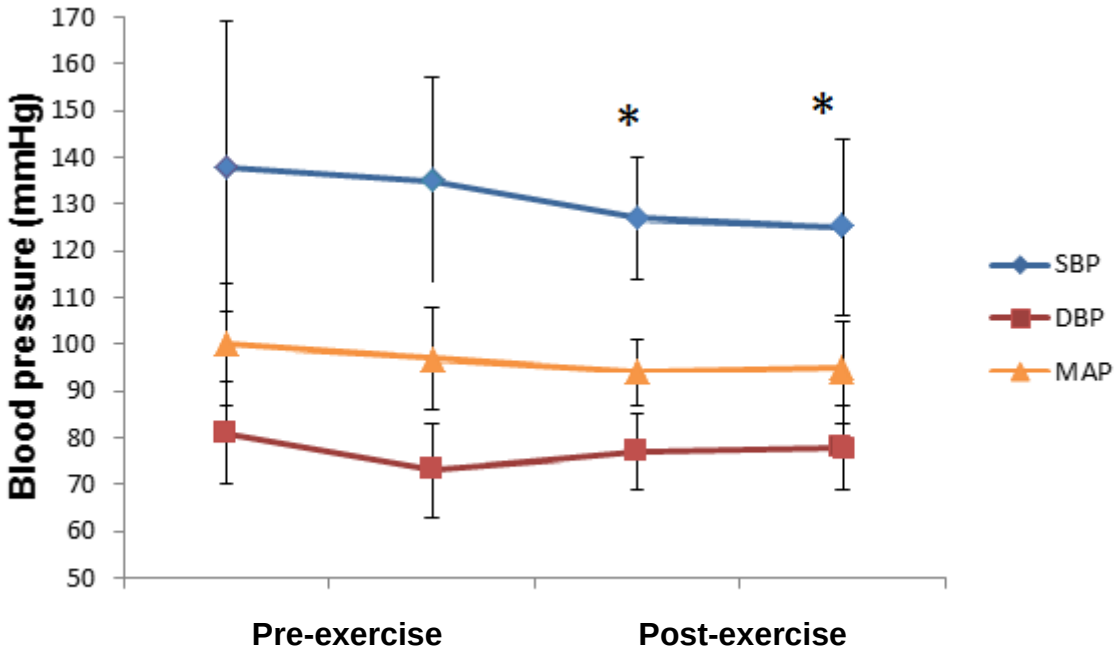
Hemodynamic variables (BP and HR) are shown in Table 7. Significant reduction in systolic BP is observed five and thirty minutes after a HIIT session regarding the measurement performed at moment 1 (pre-assessment of EF). Figure 4 shows the variation of SBP in the four moments of verification. There was no difference in DBP and MBP before and after HIIT. HR increased five minutes after exercise, returning to baseline within a period of 30 minutes.

Table 7: Hemodynamic variables before and after the exercise session.

	Pre-exercise		Post-exercise	
Variable	1	2	3	4
SBP (mmHg)	138 ± 31	135 ± 22	127 ± 13*	125 ± 19*
DBP (mmHg)	81 ± 11	73 ± 10	77 ± 8	78 ± 9
MAP (mmHg)	100 ± 13	97 ± 11	94 ± 7	94 ± 11
HR (mmHg)	63 ± 11	68 ± 10	81 ± 14 *	73 ± 10

Data are reported as mean ± standard deviation. 1 and 2: pre-exercise (pre-assessment of endothelial function; immediately HIIT pre-session); 3 and 4: post-exercise (5 and 30 minutes of HIIT session); SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate. * p<0.05.

Figure 4: Variation of systolic, diastolic, and mean blood pressure, before and after High Intensity Interval Training session.



1) pre-assessment of endothelial function; 2) pre-session of HIIT; 3) 5 minutes post TIIH session; 4) 30 minutes post TIIH session. SBP: systolic blood pressure; DBP: diastolic blood pressure; MBP: mean blood pressure. * p<0.05

Discussion

This is the first study to demonstrate that a HIIT session is effective in promoting significant subacute increase in the diameter of the brachial artery, which is accompanied by significant reduction in systolic BP in patients with HFpEF. However, after 30 minutes of this single session of interval workout, EF does not change markedly as could be expected.

Borlaug et al. (35) demonstrated that patients with HFpEF have global dysfunction in cardiovascular reserve, and the behavior of arterial vessels is one of the contributing factors, e.g., for limited functional capacity in this subgroup of patients. A finding that is also evidenced in our experiment (peak VO_2 average 18.4 3,16 $mL.kg^{-1}.min^{-1}$).

Even with changes in basal VF, patients with HFpEF who composed our sample showed vasodilation after a single session of HIIT. This finding suggests that this type of exercise can be a stimulus capable of promoting subacute systemic vasomotor changes even in patients with a substrate of chronic vascular dysfunction.

Investigating five healthy young men, Birk (36) et al. described the influence of shear stress in the VF of upper limbs not exercised in response to continuous submaximal exercise performed for 30 minutes with the lower limbs. The subjects cycled at 80% of maximum load. As a result the authors suggested that there was a transient increase in the VF of limbs not exercised, which was at least in part, mediated by shear stress.

Subsequently, the same group of researchers evaluated the vascular responses before and immediately after exercise sessions at different intensities. In this study, 10 healthy men performed 30 minutes of exercise on a cycle ergometer at 50, 70 and 85% HR max. There was an increase in shear stress and the diameter of the brachial artery immediately after exercising at all intensities proposed. It was observed that vasodilation occurred in a greater extent after exercising at higher intensities. However, the authors point out that in higher intensities of effort EF resulted in being attenuated, suggesting an inverse association between intensity

and EF (37). We point out that the evaluations carried out in this study occurred immediately after cessation of exercise.

There are discrepancies in the results available in the literature with regard to vascular responses after an exercise session. Indeed, there seems to be a biphasic behavior in EF. This hypothesis suggests that between the end of the exercise up to 60 minutes after FMV is reduced, an exponential increase occurs from this time on, which may continue for up to 24 hours (38).

Zhu et al. (39) evaluated the vascular responses in young obese individuals 60 and 120 minutes after 45 minutes of continuous exercise on a treadmill at 85% HR max. The authors found that in these subjects with endothelial dysfunction at rest, the diameter of the brachial artery was already increased one hour after the exercise session, dilating even more after the second hour. Concurrently, FMV also increased as the evaluations were being conducted (pre-exercise: 7.3 ± 3.5%; 1 hour post-exercise: 9.5 ± 4.0%; 2 hours post-exercise: 11.0 ± 4.3%; $p = 0.0004$).

Tyldum et al. (40) demonstrated that a HIIT session promotes improvement in VF, which continues up to at least 18 hours after a session of this type of exercise. To do this, they evaluated the FMV in the brachial artery in 8 healthy subjects before and after a hyperlipidemic meal preceded by a rest period (control) and one HIIT and MICT session. The session control or of exercise was carried out 16-18 hours before the meal and the FMV assessed before the meal, 30 minutes, 2 and 4 hours thereafter. Both exercise sessions increased FMV assessed 16-18 hours after its completion, while there was no change in the control group. Likewise, the exercise performed at two intensities attenuated endothelial dysfunction induced by postprandial lipemia. The major finding of the study was that HIIT session not only prevented reduction as well as improved the EF in these individuals. The authors of the experiment concluded that a HIIT session is able to contribute to vascular integrity for hours after completion of the exercise, the response being dependent on the intensity of the effort.

In turn, when analyzing the results in VF subacute studies of individuals exposed to HIIT, possible beneficial effects of a single exercise session have been observed. Hallmark et al. (25) evaluated the sub-acute responses to exercise in VF for 14 eutrophic individuals and 9 obese subjects. They performed 30 minutes of HIIT

and MICT sessions. EF was assessed at baseline, one, two, and four hours post-exercise. After HIIT session, the eutrophic subjects showed increase in FMV in relation to the index checked at baseline, while the MICT session did not promote significant changes in VF. In contrast, the obese subjects showed an increase in FMV after both physical training sessions (HIIT and MICT).

Some studies have evaluated the sub-acute responses to exercise in individuals with cardiovascular disease. Currie et al. (23) investigated changes in EF in 10 active individuals, all with stable CAD, aged between 55 and 77 years and endothelial dysfunction at rest. After a single session of HIIT, there was significant improvement in EF of these patients 60 minutes post-exercise (absolute difference in artery diameter, pre: 0.25 ± 0.13mm; post: 0.29 ± 0.13mm). In a second study(24), this same Canadian group, 19 men with stable ischemic heart disease, aged between 55 and 71 years, had four series of 3 minutes on a cycle ergometer at increasing loads (20%, 40%, 60%, and 80% of peak load previously identified in maximal exercise test). In this investigation, the assessment was carried out only 15 minutes after the exercise series and two different types of response were observed: improved EF only occurred in those subjects with lower FMV when at rest.

Going against the aforementioned studies, we found no improvement in EF in patients with HFpEF. It is possible that this may have occurred, since we evaluated patients only after 30 minutes of HIIT session. It seems that the time period may be a key factor which may have contributed to the discrepancy between our findings and those of Currie et al. (23) on ischemic heart disease (evaluation after 60 minutes) or Hallmark et al. (25) in obese subjects (evaluation after 60, 120, and 240 minutes).

As there is a total lack of studies regarding patients with HFpEF, we do not know exactly what the EF behavior is at different time points over 24 hours after one HIIT session. It is interesting to note that, just as our patients showed no improvement in FMV 30 minutes after a HIIT session, we also did not observe improvement in EIV after administration of NTG. Although there are few studies that evaluated the subacute effect of a workout in EIV, most of them also showed there is no change in this outcome (23,41,42).

It's worth noting that the reduction in EF after workout is not necessarily associated with a negative chronic adaptation. During exercise there is an increase in oxidative stress and this is one of the mechanisms that may explain reduced EF immediately after workout (38). Suvorava et al.(43) present the hypothesis that sharply generated increase of vascular oxidative stress in each session of exercise training is reduced as summation of the sessions occurs. These oxidative stress peaks are important in signaling endothelial cells to induce the expression of antioxidant enzymes such as nitric oxide synthase (eNOS), which is a key element of synthesis and release of NO. Thus, the chronic adaptations in VF can be explained, in part, by the reduction of reactive oxygen species (ROS) and best antioxidant capacity of the vascular wall (44). In short, while a workout can increase vascular oxidative stress, regular physical training seems to protect the vasculature against permanent oxidative stress.

Blood pressure

The hypotensive effects of interval exercise is already well established in the literature. Exercise performed at submaximal intensities closer to the peak of effort promotes greater and longer reduction in BP than performed at lower intensities (45). This fact makes HIIT an attractive and potentially beneficial method even in the context of HFpEF, being well tolerated even by individuals with limited functional capacity, as demonstrated in this study and others that enroll patients with different pathologies (22-26,46).

Chan et al.(47) showed that even in individuals with normal BP (SBP: 117 ± 8mmHg; DBP: 84 ± 6mmHg), a HIIT session with sprints on a cycle ergometer was effective in significantly reducing blood pressure levels two hours after exercise (SBP: 109 ± 8mmHg; DBP 77 ± 5mmHg).

In turn, it is known that hypertensive patients tend to have higher hypotensive response to aerobic exercise. Ciolac et al. (26) evaluated ambulatory BP of hypertensive patients who performed a HIIT session and another of MICT on the cycle ergometer. The authors showed that both sessions reduced BP and the

percentage of subjects with normal BP levels over 24 hours after exercise was significant.

The effects of HIIT and MICT session on the magnitude and duration of hypotensive response in hypertensive patients by ambulatory blood pressure monitoring was also evaluated (46). In this case the exercises were performed on a treadmill. The MICT session comprised 42 minutes at the intensity corresponding to the 1st ventilatory threshold. In turn, the HIIT session consisted of alternating blocks of 4 minutes in the 2nd ventilatory threshold and recovery at 40% of VO_2max. Hypotension was noted after exercise sessions with a significant reduction in SBP, DBP, and MAP. Comparing the effect of exercise sessions, we observed that the HIIT session promoted greater magnitude of hypotension with lower cardiovascular overhead measured by the double product.

There are different possibilities for prescription interval workout. Angadi et al. (48) compared the hypotensive effect of MICT session and two distinct high-intensity interval exercise protocols. The first comprised the execution of four 4-minute blocks of alternate exercise for 3 minutes of active recovery (protocol similar to that used in our study and referred to as HIIT). The second interval exercise protocol consisted of six sprints of 60 seconds combined with active recovery, called interval training sprints (ITS). Finally, the MCTI session was held at 75-85% HR max. All exercise sessions were held on a cycle ergometer and compared to a control session (without exercise). BP was checked before and every 15 minutes until the third hour of exercise sessions. During the three hours after the different sessions of exercise, both SBP and DBP were reduced compared to the control session. However, the post-exercise hypotension was more significant after the HIIT session.

In our study, we observed an absolute reduction of 13 mmHg in SBP thirty minutes after the workout. We measured BP four different times (twice at rest and twice after HIIT), noting that before the assessment of VF, 56% of patients had SBP > 135 mmHg. This figure dropped to 31% just before the workout, significantly reducing to 6% and 18%, five and thirty minutes after exercising, respectively.

There was no significant difference in both DBP as in MBP. In this regard, physical activities that have an important dynamic component associated (as was the

case of HIIT applied to the subjects of this sample), usually do not significantly change the diastolic BP, as well as the mean BP.

Limitations

This is an effectiveness trial that includes a small and heterogeneous sample of patients with HFpEF. The presence of diabetes, atherosclerosis, gout, and tobacco use may have influence on the EF (49). However, we chose not to exclude patients with these comorbidities from the study, given that the first two in particular are highly prevalent in individuals with HFpEF (4).

It is worth mentioning that the two gout patients in our sample showed a constrictive response of great magnitude to the evaluation of FMV after exercising (more pronounced than the other patients). Evidence suggests that excessive uric acid affects the bioavailability of NO by inducing endothelial dysfunction (50). In this regard, it is possible that an intervention with regular sessions and chronic bases of HIIT can benefit EF in individuals with gout.

A HIIT session was a stimulus able to promote vasodilation and reduction of BP in patients with HFpEF 30 minutes after the completion of the exercise. However, we do not know if that stimulus is also effective in improving EF and BP in the subsequent hours. To this end, repeated measurements over time are necessary in order to know what is the actual behavior of these variables in the course of time.

We did not measure blood flow. Such measurement would allow us a greater understanding of the hemodynamic responses against the physical stress in these patients, besides allowing the estimation of shear stress. It is known that shear stress and the diameter of the brachial artery influence EF (51) and therefore, the control of these covariates is suggested for future experiments.

Finally, the presence of a control group of matched individuals without HFpEF could help establish what responses can be attributed to the syndrome under study. As well as a control session without exercise would report more accurately that the verified answers really are, in fact, the protocol result of the proposed exercise.

Future perspectives

Our research provides new information about the subacute effect of a single HIIT session of VF and BP in patients with HFpEF. The next step, regarding a single session, is to analyze the responses in the DBA, EF and BP immediately, 15, 60 minutes, and up to 24 hours.

In an even more ambitious scenario, a randomized clinical trial will be relevant to the present chronic adaptations to HIIT in these same outcomes and in others that may be of interest with this population, such as functional capacity and quality of life, besides identifying the impact of such training on morphological and functional changes in the myocardium.

Conclusion

After 30 minutes of a single HIIT session the DBA increases, BP reduces, but there is no significant change in the FMV in patients with HFpEF. These findings go in the direction that this type of training can be effective in this complex clinical syndrome, but studies to assess the time course of the VF and BP are needed.

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