“DIFERENTES MODALIDADES DE TREINAMENTO FÍSICO EM PACIENTES PÓS-TRANSPLANTE CARDÍACO: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE EM REDE”

Tese

Juliana Beust de Lima

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares

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Autora: Ma. Juliana Beust de Lima

Orientador: Prof. Dr. Ricardo Stein

Tese submetida como requisito para obtenção do grau de Doutora 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

2021

CIP - Catalogação na Publicação

Beust de Lima, Juliana
DIFERENTES MODALIDADES DE TREINAMENTO FÍSICO EM PACIENTES PÓS-TRANSPLANTE CARDÍACO: UMA REVISÃO SISTEMÁTICA COM META-ANÁLISE EM REDE / Juliana Beust de Lima. -- 2021.
197 f.
Orientador: Ricardo Stein.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares, Porto Alegre, BR-RS, 2021.

1. Transplante cardíaco. 2. Treinamento físico. 3. Consumo de oxigênio de pico. 4. Eventos adversos. 5. Qualidade de vida. I. Stein, Ricardo, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

AGRADECIMENTOS

Ao meu amigo e mentor, Prof. Dr. Ricardo Stein, pelo privilégio da sua orientação desde a Iniciação Científica. Obrigada por tão cedo confiar na jovem estudante de Educação Física e oportunizar uma trajetória acadêmica de tanto aprendizado clínico e científico. Obrigada por estar sempre acessível e disposto a ensinar. Sobretudo, obrigada por ser a referência que és para mim.

Aos demais professores, colegas e amigos com os quais compartilho a autoria deste estudo pelo interesse genuíno, comprometimento e companheirismo. As inúmeras horas de estudo e trabalho com vocês, além de produtivas foram muito gratificantes. Sou grata pela forma que conduzimos este estudo, com rigor metodológico em um ambiente de ensino/aprendizagem muito amistoso e motivador. Vocês são inspirações para mim: Me. Douglas dos Santos Soares, Me. Filipe Ferrari, Me. Nelson Carvas Junior, Gabriel Carvalho, Prof. Dr. Santiago Alonso Tobar Leitão, Ma. Lívia Adams Goldraich e Profa. Ma. Nadine Clausell.

Ao Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares, à Universidade Federal do Rio Grande do Sul e ao Hospital de Clínicas de Porto Alegre pela oportunidade de desenvolver pesquisa científica de alto nível e aprender com grandes Professores.

Aos meus pais, Márcia Eliane Beust de Lima e Orlando Pires de Lima, pelo amor que sempre me fizeram sentir e transpor ao que me dedico. Obrigada pelo apoio nas mais diversas situações e aconselhamentos tão importantes. Obrigada pela educação formal e através do exemplo. Obrigada pelo incentivo e amizade.

SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

VO_2 pico - consumo de oxigênio de pico

DC - débito cardíaco

Dif a-v O_2 - diferença arteriovenosa de oxigênio

DVE - doença vascular do enxerto

VE/VCO_2 *slope* - ventilação minuto relativa à produção de dióxido de carbono

ECR - ensaio clínico randomizado

FC - frequência cardíaca

IC - insuficiência cardíaca

ISHLT - *International Society for Heart and Lung Transplantation*

OUES - *oxygen uptake efficiency slope*

Pulso de O_2 – pulso de oxigênio

RCV - reabilitação cardiovascular

TxC - transplante cardíaco

TC - treinamento combinado

TCM - treinamento contínuo moderado

TCPE - teste cardiopulmonar do exercício

TF - treinamento físico

TIAI - treinamento intervalado de alta intensidade

TR - treinamento resistido

RESUMO

Os objetivos desta revisão sistemática com meta-análise em rede foram comparar a segurança e eficácia de diferentes modalidades de treinamento físico (TF) na melhora do consumo de oxigênio de pico (VO_2 pico) e sobre outros desfechos relevantes em pacientes pós-transplante cardíaco (pós-TxC). Foram incluídos ensaios clínicos randomizados envolvendo pacientes pós-TxC com a presença de pelo menos um grupo de TF, que pode ser comparado com outra modalidade de treinamento e/ou um grupo controle sem exercício. Realizamos uma pesquisa bibliográfica abrangente, avaliamos o risco de viés (RoB 2.0), assim como a certeza na evidência (CINeMA). Moderada certeza na evidência sugere que pacientes submetidos à treinamento combinado e treinamento intervalado de alta intensidade, comparados aos cuidados usuais, provavelmente apresentam um aumento em média de 3,49 (IC 95% 1,96 a 5,02) e 4,78 (IC 95% 1,88 a 7,69) $mL.kg^{-1}.min^{-1}$ na capacidade funcional representada pelo VO_2 de pico, respectivamente. Nesse contexto, é provável que estas sejam as modalidades de TF mais eficazes na melhora da capacidade funcional nesta população. Embora os dados sejam limitados, nenhum evento adverso relacionado ao treinamento foi relatado.

ABSTRACT

The objectives of this systematic review with network meta-analysis were to compare the safety and efficacy of different modalities of exercise training (ET) in improving peak oxygen consumption (VO_2 peak) and on other relevant outcomes in heart transplant (HTx) recipients. Randomized clinical trials involving HTx recipients with the presence of at least one ET group were included, which can be compared with another training modality and / or a control group without exercise. We performed a comprehensive literature search, assessed the risk of bias (RoB 2.0), as well the certainty in the evidence (CINeMA). Moderate certainty in the evidence suggests that patients undergoing combined training and high intensity interval training, compared to a control group, probably have a mean increase of 3.49 (95% IC 1.96 to 5.02) and 4.78 (95% IC 1.88 to 7.69) ml. $kg^{1}min^{-1}$ in the functional capacity represented

by VO_2 peak, respectively. In this context, it is likely that these are the most efficacious modalities of ET in improving functional capacity in this population. Although data are limited, no exercise-related adverse events have been reported.

INTRODUÇÃO

O transplante cardíaco (TxC) é o tratamento padrão ouro para pacientes selecionados com insuficiência cardíaca (IC) em estágio terminal.[1,2] Embora este procedimento possa melhorar a qualidade e prolongar a expectativa de vida,[3,4] o que é extremamente relevante, muitos pacientes persistem com capacidade funcional reduzida concomitante a presença de complicações e comorbidades.[5,6]

A reduzida capacidade funcional, mensurada pelo consumo de oxigênio de pico (VO_2 de pico), ocorre devido a prejuízos em componentes centrais (cardíaco e pulmonar) e periféricos (músculo esquelético e vascular).[6] Este conjunto de alterações, por sua vez, pode ser atribuído a combinação dos seguintes fatores: (a) consequências multissitêmicas da IC prévia, (b) cirurgia de grande porte e evolução clínica pós-procedimento, (c) terapia imunossupressora e (d) ausência completa ou parcial de inervação cardíaca.[7-9] Compreender os fatores que contribuem para a menor capacidade funcional, assim como identificar comorbidades prevalentes em pacientes pós-TxC, auxilia no direcionamento de estratégias que possam favorecer a uma melhor qualidade de vida e prognóstico.

Neste cenário, a reabilitação cardiovascular (RCV) com ênfase em treinamento físico (TF) é estratégia segura e altamente recomendada.[10-14] Evidências sugerem benefícios multifatoriais de diferentes modalidades TF em pacientes pós-TxC, melhorando a capacidade funcional e repercutindo positivamente em respostas fisiológicas que podem auxiliar no controle dos fatores de risco cardiovasculares e atenuar os efeitos adversos da terapia imunossupressora.[6,8,9] Pequenos ensaios clínicos randomizados (ECRs) demostraram eficácia do TF na melhora do controle autonômico (cardíaco e periférico),[15] níveis pressóricos,[16] composição corporal e força muscular esquelética[17] neste grupo de indivíduos. Apesar de alguns estudos apresentarem resultados divergentes, evidências demonstram o potencial do exercício em promover melhora em parâmetros cronotrópicos,[18] função endotelial[19] e eficiência ventilatória.[20] Além disso, através de uma revisão sistemática com meta-análise da Cochrane,[21] verificou-se a eficácia da intervenção em aumentar o VO_2 pico, permanecendo

incerto o efeito da estratégia sobre a qualidade de vida relacionada à saúde, o que possui benefício consolidado em pacientes com IC.[22]

Diante das evidências disponíveis, a importância do encaminhamento de pacientes pós-TxC à programas de RCV com ênfase em TF se faz inexorável. Contudo, o melhor manejo da intervenção será possível através de conhecimento que venha ultrapassar: (a) a fisiopatologia e manejo da condição clínica, (b) respostas fisiológicas ao exercício, (c) cuidados e avaliações necessárias e (d) diferentes possibilidades de prescrição de exercício e respectivos efeitos clínicos.

REVISÃO DA LITERATURA

Panorama do transplante cardíaco e perspectivas com o treinamento físico

O TxC, concomitante a um complexo arsenal terapêutico e rede de cuidados, representa a muitos pacientes com IC avançada a oportunidade de prosseguir com a vida. Décadas de esforço árduo, resiliência e investimento em pesquisa científica possibilitaram a melhor compreensão e inovação sobre os diferentes fatores envolvidos no processo e que contribuem para o sucesso contemporâneo nessa área do conhecimento.[2,23]

O primeiro procedimento entre humanos, liderado pelo Professor Cristian Barnard, aconteceu na África do Sul em dezembro de 1967.[24] Seis meses após, o Brasil integra-se a este pioneirismo com a realização do primeiro TxC no país realizado pela equipe do Doutor Euryclides Zerbini no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo.[25] Desde então, e especialmente a partir do advento da ciclosporina na década de 80, o procedimento é difundido pelo mundo e torna-se cada vez mais frequente.[2] No ano de 2017 foram registrados mais de 5.500 TxCs no mundo, enquanto no Brasil, o maior marco nacional com o relato de 378 procedimentos.[4,26] No Hospital de Clínicas de Porto Alegre, entre 2015 e 2020, foram realizados 66 TxCs, com recorde de 16 cirurgias no ano de 2016.

Conforme registros da *International Society for Heart and Lung Transplantation* (ISHLT), 126.753 TxCs foram realizados entre os anos de 1982 e 2015. Entre os adultos que realizaram o procedimento neste período, a mediana de sobrevida foi de 10,7 anos, o que se observa maior nos anos mais recentes.[27] Entre os anos de 2002 e 2009 a sobrevida verificada foi de 12,5 anos com estimativa ainda superior, 14,8 anos, entre aqueles que atingiram o primeiro ano pós-TxC.[4] A evolução clínica neste período, até um ano após o procedimento, é de grande relevância prognóstica e a redução na mortalidade observada nas últimas décadas é atribuída a melhora da sobrevida neste intervalo de tempo. No entanto, segundo análises disponibilizadas pela ISHLT, este comportamento não foi observado em relação a sobrevida após um ano da cirurgia. Estes achados sugerem que a melhora na expectativa de vida pós-TxC nos anos vindouros possa ocorrer a partir de intervenções direcionadas aos processos responsáveis pela mortalidade a longo prazo, entre os quais destacam-se a doença vascular

do enxerto (DVE), disfunção renal e neoplasia maligna. Ademais, outras comorbidades são altamente prevalentes e devem ser manejadas, tendo em vista que entre os pacientes que sobrevivem pelo menos cinco anos, 90% apresentam hipertensão, 91% dislipidemia e 40% diabetes. [28]

A indicação para o TxC deve considerar a relação-risco benefício, e para isso uma avalição abrangente, incluindo aspectos clínicos, laboratoriais, hemodinâmicos, psicológicos e sociais é primordial. [29] Neste âmbito, a obtenção de informações refinadas auxilia na identificação dos casos que mais necessitam do procedimento, ao passo que também apresentem alta probabilidade de prognóstico favorável durante e após a cirurgia.[30] Candidatos habituais são pacientes IC estágio D com sintomas progressivos refratários a melhor terapia medicamentosa e intervencionista disponível. Tipicamente apresentam prognóstico adverso, severa limitação funcional (NYHA III e IV), dependência de drogas inotrópicas e/ou suporte circulatório mecânico, arritmias ventriculares sintomáticas recorrentes, assim como doença isquêmica com angina sem possibilidade de revascularização.[29]

Na avaliação prognóstica, que também pode ser realizada através de escores, o Teste Cardiopulmonar do Exercício (TCPE) desponta como ferramenta de grande utilidade clínica, uma vez que possibilita a avaliação objetiva da capacidade funcional através da mensuração dos principais preditores prognósticos na IC, como o VO_2 pico e a relação entre a ventilação e a produção de dióxido de carbono, expressa como inclinação VE/VCO_2 (VE/VCO_2 *slope*). De acordo com diretrizes nacionais e internacionais, são considerados critérios para indicação ao TxC: VO_2 pico ≤12 $ml.kg^{-1}.min^{-1}$ (≤14 $ml.kg^{-1}.min^{-1}$ em intolerantes à betabloqueadores), VO_2 pico ≤50% do previsto em pacientes com <50 anos e mulheres, VO_2 pico ajustado para massa magra ≤19 $ml.kg^{-1}.min^{-1}$ em pacientes com índice de massa corporal >30, assim como VE/VCO_2 *slope* >35 quando somente teste submáximo for possível (R<1,05).[29,30,31]

Avanços expressivos ocorreram ao longo da história do TxC e compreendem (a) a melhor seleção e (b) manejo dos pacientes ainda no período pré-operatório, (c) avanços na técnica cirúrgica e (d) cuidados perioperatórios, (e) melhor preservação do órgão doado, (f) avaliação do risco imunológico e (g) introdução de novos agentes de imunossupressão, bem como (h) aprimorado monitoramento da função do enxerto e (i) vigilância de complicações a

longo prazo. Conjunto de condutas que repercute em resultados cada vez mais satisfatórios.[2,23,32]

Em relação a técnica cirúrgica, por muito tempo se realizou a técnica pioneira desenvolvida por Lower e Shumway através da abordagem clássica com anastomoses biatriais. No entanto, na década de 90, Yacoub e Banner propuseram alteração na técnica com a realização de anastomoses bicavais, visando a preservação da geometria do átrio direito, bem como da função mecânica e eletrofisiológica atrial.[33] Desde então, observa-se crescente o número de cirurgias realizadas com a nova técnica, sendo a mais frequente nos dias de hoje.[34] A preferência se justifica pelos melhores desfechos observados, como a menor incidência de arritmias atriais e disfunção valvar atrioventricular,[33] necessidade inferior de implante de marca-passo permanente, assim como maior sobrevida.[34]

Com o estabelecimento de técnicas cirúrgicas e métodos para preservação do órgão, também foi necessário o desenvolvimento de métodos para avaliação da rejeição do aloenxerto, bem como terapias eficazes na prevenção e tratamento desses episódios desfavoráveis.[2] A rejeição do aloenxerto, por sua vez, é classificada em três tipos principais hiperaguda, aguda e crônica e caracteriza-se pela infiltração inflamatória de linfócitos e macrófagos no tecido cardíaco, processo mediado pelas células T ou anticorpos e que gera dano celular.[2,23,35] Neste cenário, grande avanço foi possível através da biópsia endomiocárdica, que possibilitou a análise patológica de pequenos pedaços do miocárdio retirados por acesso percutâneo.[2] Desde então, é considerado o método padrão ouro na avaliação da rejeição aguda e atualmente diagnosticada a partir de graus que variam de nenhuma rejeição (R0) à rejeição severa (R3).[35] Considerando que o risco de rejeição aguda é maior nos primeiros meses pós-TxC, as biópsias de rotina via transjugular são realizadas com maior frequência neste período, permanecendo necessárias, mas tornando-se mais espaçadas com o decorrer do tempo. O resultado obtido nas análises pode sugerir requerimento de exames complementares, assim como evidenciar a necessidade de manejo no tratamento imunossupressor ao se considerar cada caso de forma individual.[2,23]

O ajuste fino e permanente na imunomodulação é necessário e visa suprimir suficientemente o sistema imune para prevenção da rejeição do aloenxerto. Ao mesmo tempo, deve ser administrado de forma a tentar evitar os efeitos adversos da imunodeficiência, assim como de toxicidade (infecções, neoplasias, insuficiência renal,

dislipidemia, diabetes e hipertensão). Para tanto, na maioria dos casos, a terapia tripla é adotada com o regime simultâneo de três classes de drogas: corticosteroides, inibidores da calcineurina (tacrolimos ou ciclosporina) e agentes antiproliferativos (micofenolato de mofetil ou azatioprina).[32] Inibidores do sinal de proliferação (everolimus ou sirolimus) representam a mais recente classe de fármacos e tem sido adotada em um subgrupo de pacientes pós-TxC.[4,32]

Em consonância aos cuidados mencionados, o TxC destinado aos candidatos adequadamente selecionados está associado a melhora dramática na sobrevida, qualidade de vida[27] e capacidade funcional,[37] possibilitando em muitos casos o retorno ao trabalho[38] e até mesmo o envolvimento em atividades esportivas competitivas.[39] Comparados ao período prévio à cirurgia, os pacientes pós-TxC apresentam menos sofrimento relacionado aos sintomas, melhor percepção de saúde, melhor *status* funcional e maior satisfação geral com a vida. No entanto, é oportuno destacar que a despeito da expressiva melhora, certo grau de limitação funcional e percepção de sintomas pode permanecer.[3] Em média, os pacientes pós-TxC apresentam capacidade funcional, avaliada através do VO_2 pico, abaixo do predito, o que decorre devido à múltiplos fatores: condição de IC prévia, terapêutica imunossupressora necessária e fisiopatologia do coração transplantado.[6]

Compreender os fatores que contribuem para menor capacidade funcional, assim como identificar a presença de comorbidades prevalentes em pacientes pós-TxC auxilia no direcionamento de estratégias que possam ser favoráveis. Neste cenário, a RCV passa a ser recomendada. A partir de uma abordagem multidisciplinar, ela visa auxiliar na promoção da saúde global do indivíduo, para que este possa, através dos seus próprios meios, ocupar um lugar tão normal quanto seja possível na sociedade. Entre as múltiplas estratégias que devem ser integradas nestes programas, o TF assume papel central.[10,12] ECRs publicados a partir da década de 90, têm apontado o método como estratégia eficaz na melhora de inúmeros fatores associados a fisiopatologia do paciente pós-TxC.[10]

Neste cenário, a compreensão aprofundada da fisiologia integrativa do exercício nessa população se faz fundamental na promoção de intervenções seguras. Ademais, possibilita a exploração das potenciais adaptações advindas do TF que possam favorecer desfechos positivos em pacientes pós-TxC.

Exercício físico pós-transplante cardíaco: condições clínicas e respostas fisiológicas

A partir da melhora acentuada na hemodinâmica cardíaca, pacientes pós-TxC experimentam melhor qualidade de vida[3,39] e maior capacidade funcional.[36] No entanto, alguns estudos demonstram que a despeito do aumento expressivo e desejado no VO_2 pico (≈5 $ml.kg^{-1}.min^{-1}$ no primeiro ano)[40], este permanece abaixo do predito[41] e é menor nos pacientes pós-TxC quando comparados aos pares de mesma idade sem IC.[6,24,25,36]

O prejuízo observado na tolerância ao exercício nestes pacientes é atribuído à inúmeros fatores, que por sua vez podem ser elucidados a partir de conceitos básicos da fisiologia do exercício.[6,9] A Equação de Fick evidencia a contribuição de componentes centrais e periféricos para tolerância ao exercício, onde consumo de oxigênio é produto do débito cardíaco (DC) pela diferença arteriovenosa de oxigênio (Dif a-v O_2). Por sua vez, a teoria ilustrada pelas Engrenagens de Wasserman ressalta a interdependência dos diferentes sistemas fisiológicos na captação, transporte e extração de oxigênio, processo que possibilita a ressíntese de ATP por via oxidativa para contração muscular. Sendo assim, é evidente a contribuição de múltiplos componentes - ventilação pulmonar, DC, pré-carga, pós-carga, inotropismo, cronotropismo, dromotropismo, volume sanguíneo, concentração de hemoglobina, fluxo sanguíneo periférico, e capacidade metabólica celular - nas adaptações do organismo frente às diferentes demandas metabólicas, bem como no VO_2 pico.[42,43] Em pacientes pós-TxC, apesar do novo órgão apresentar função sistólica preservada, alterações decorrentes do processo patológico e até mesmo efeito das intervenções terapêuticas necessárias repercutem em diferentes níveis supracitados, podendo trazer prejuízos. [6,9]

Considerando-se que o período prolongado de IC culmina em alterações em diferentes sistemas fisiológicos, a compreensão da fisiopatologia da síndrome auxilia na identificação de fatores que podem persistir como limitadores ao exercício mesmo após o TxC. Por exemplo, observa-se em pacientes com IC hiperatividade no Sistema Nervoso Autônomo Simpático e no Sistema Renina Angiotensina Aldosterona. Inicialmente a maior atividade destes sistemas visa compensar o baixo DC e garantir a perfusão sanguínea tecidual. No entanto, a longo prazo a exacerbação neuro-humoral é deletéria e afeta diferentes respostas reflexas.[44,45] Embora haja relato de redução na atividade simpática nervosa muscular nos meses seguintes ao TxC,[46]

Houssierre et al. observaram que a mesma está aumentada, tanto em repouso quanto em exercício, nos pacientes transplantados há pelo menos quatro anos em comparação aos indivíduos saudáveis. Ademais, a resposta metaborreflexa exagerada e o aumento na sensibilidade dos quimiorreceptores, associaram-se a alterações ventilatórias durante o TCPE, verificadas através da ventilação de pico e relação VE/VCO_2 *slope*.[47]

Nos pacientes com IC, além das alterações cardíacas e no controle autonômico, observam-se alterações pulmonares e periféricas que também contribuem para intolerância ao exercício, como: a) fraqueza muscular inspiratória, b) redução na difusão alvéolo-capilar, c) disfunção endotelial, d) redução na densidade capilar e e) anormalidades estruturais e funcionais que configuram a miopatia esquelética.[48,49] Estas alterações na musculatura esquelética, compreendem redução na quantidade e qualidade muscular, assim como maior proporção de fibras musculares do tipo II e menor quantidade e atividade mitocondrial, contribuindo em conjunto para uma musculatura mais predisposta à fadiga.[48]

A miopatia esquelética provavelmente resulta da combinação entre as perturbações sistêmicas com a inatividade física, ambas inerentes ao agravamento da IC.[48] Ainda neste âmbito, cabe ressaltar que a sarcopenia, redução da massa e força muscular, é altamente prevalente na síndrome e está independentemente associada a um menor VO_2 pico,[50] bem como a um pior prognóstico.[51,52] De forma controversa, na ausência de intervenções direcionadas, estas alterações podem ser agravadas no período pós-TxC. Isso ocorre majoritariamente devido à utilização dos corticosteróides e inibidores da calcineurina, que por sua vez apresentam efeitos deletérios já conhecidos sobre a saúde vascular, musculatura esquelética e densidade mineral óssea. [6,8,9]

No estudo de Braith et al., verificou-se que dois meses após o TxC, a composição corporal dos pacientes encontra-se piorada, com aumento na massa gorda e redução na massa livre de gordura em relação ao período pré-TxC, havendo ainda piora progressiva nestes componentes no transcorrer do tempo.[53] Ainda no primeiro ano após o TxC, Schaufelberger et al. observaram persistente transição de fibra muscular do tipo I para o tipo II e capilarizarão muscular inferior à observada nos indivíduos controles.[54] Em contrapartida, no seguimento pós-TxC, verificou-se melhora na área de secção transversa do músculo vasto lateral,[54,55] assim como na atividade enzimática oxidativa e glicolítica,[55] enquanto permanece incerta qual a evolução da variável força muscular.[53,54] No entanto, é reconhecido que os pacientes

persistem com força muscular de membros inferiores prejudicada, o que por sua vez apresenta forte correlação com o VO_2 pico, podendo explicar, ao menos em parte, a limitada capacidade funcional.[56,57] À corroborar com estes achados, embora dispneia seja o principal sintoma limitante ao TCPE antes do TxC, após o procedimento, os pacientes relatam interrupção do exercício devido à fadiga nos membros inferiores e exaustão muscular.[36]

Intervenções com potencial de melhorar a qualidade e expectativa de vida após o TxC são necessárias e devem auxiliar na prevenção dos efeitos nocivos dos imunossupressores. Além de comprometerem a saúde óssea e muscular esquelética, contribuem para o desenvolvimento de comorbidades, como diabetes, dislipidemia e hipertensão,[2] que em conjunto com as respostas imunológicas, são fatores de risco para DVE, uma das principais causas de morte após um ano do procedimento.[28,58] O processo do desenvolvimento da DVE é complexo e multifatorial, causando inflamação, disfunção e lesão no endotélio vascular que repercute em proliferação e migração das células musculares lisas com regulação positiva das moléculas de adesão. A resposta de reparo exagerada, promove espessamento intimal concêntrico e difuso, e por consequência, estenose luminal nos vasos epicárdicos, podendo promover a isquemia responsável pela deterioração aguda ou progressiva do enxerto.[58] Neste cenário, fator agravante é a ausência de inervação do coração transplantado, o que impede a manifestação de angina, por exemplo. Assim, a identificação da isquemia torna-se um desafio.

Neste contexto, a preservação e/ou promoção da saúde vascular é relevante, o que tem como fator chave um endotélio funcional. Esse, por sua vez, é composto por uma monocamada de células achatadas e sobrepostas e recobre a luz de todos os vasos sanguíneos. Além de ser uma barreira anatômica, situada entre o sangue circulante e a camada média vascular formada por músculo liso, destaca-se por ser um órgão endócrino fundamental para integridade vascular.[59,60] As células endoteliais sintetizam e liberam, a partir de estímulos físicos (tensão de cisalhamento), neurais (acetilcolina, nitroglicerina) e humorais, substâncias vasoativas que se dividem entre fatores relaxantes e constritores derivados do endotélio. Um endotélio funcional é decorrente do equilíbrio dessas substâncias, sendo a biodisponibilidade de óxido nítrico um fator fundamental para a homeostase vascular. Quando há equilíbrio entre a síntese e remoção de NO, as células endoteliais além de regularem o tônus vascular, impedem a proliferação das células musculares lisas, inibem fatores pró-inflamatórios e a adesão celular, dificultando a formação de trombos e inflamação

da parede do vaso. Por outro lado, o desequilíbrio crônico nesse sistema pode resultar em disfunção endotelial com marcado prejuízo na vasodilatação endotélio dependente devido à redução na biodisponibilidade de NO. [61,62]

A capacidade vasodilatadora está prejudicada em pacientes pós-TxC, o que pode ser atribuído às alterações decorrentes do período de IC prévia em conjunto com o efeito dos inibidores da calcineurina, especialmente quando a ciclosporina é o fármaco de escolha, promovendo o desbalanço entre os fatores relaxantes e constritores derivados do endotélio. [63,64] Neste contexto, a função endotelial coronária pode ser um marcador importante, uma vez que evidências sugerem envolvimento na progressão da DVE.[65-67] Além disso, alguns estudos demonstram a contribuição da função vasomotora periférica na capacidade funcional diminuída apresentada pelos pacientes. Patel et al. verificaram que a dilatação mediada pelo fluxo nas artérias de condutância está associada à duração do exercício,[68] ao passo que Andreassen et al. observaram associação entre a capacidade de dilatação na microcirculação periférica com o VO_2 pico nesta população.[69] Achados de Bussières et al. vão na mesma direção, evidenciando associação entre outros componentes periféricos, como a resistência arterial periférica (pós carga) e Dif a-v O2, mensuradas durante exercício, com o prejuízo funcional.[70]

Fator preponderante na resposta deprimida ao exercício em pacientes pós-TxC são as alterações cardíacas. A despeito do novo coração apresentar função sistólica preservada, a hemodinâmica cardíaca, apesar da melhora substancial em relação ao período pré TxC, ainda está prejudicada frente às demandas metabólicas mais elevadas.[6,8,9] Kao et al. verificaram que o índice cardíaco no pico do esforço é ≈41% menor do que em indivíduos saudáveis pareados pela idade e sexo.[71] O comprometimento é primordialmente decorrente da incompetência cronotrópica devido à ausência de inervação autonômica cardíaca, tanto de fibras simpáticas quanto parassimpáticas, consequente à secção cirúrgica. Sendo assim, observa-se: (a) frequência cardíaca (FC) de repouso elevada (>90 bpm), (b) resposta deprimida na elevação da FC durante esforço progressivo, (c) menor FC de pico, (d) menor FC de reserva, (e) atraso na recuperação da FC após exercício e (e) prejuízo muito significativo na variabilidade da FC. [72,73]

A taquicardia em repouso, observada principalmente no primeiro ano pós-TxC, ocorre devido à denervação vagal, tornando o coração especialmente dependente do controle

intrínseco, enquanto a ausência de inervação simpática culmina em déficit cronotrópico com FC pico reduzida, sendo este o fator primordial na atenuação do VO_2 pico. Apesar da capacidade funcional reduzida, estima-se que o DC seja normal até esforços de moderada intensidade. De qualquer maneira, em todas as intensidades de exercício, o aumento do volume sistólico é dependente da pré-carga por meio do mecanismo de Frank-Starling, o que visa compensar a incompetência inotrópica. O volume sistólico é anormal no pico do esforço em indivíduos pós-TxC, ao passo que aumenta proporcionalmente mais do que nos pares saudáveis. Outro mecanismo que promove o aumento da FC durante o exercício, é a estimulação dos beta-receptores via catecolaminas circulantes liberados pela supra-renal,[72,73] sem necessariamente ser superior ao observado nos indivíduos saudáveis.[74]

Em pacientes recentemente transplantados, normalmente a FC permanece aumentando mesmo após a interrupção do exercício. Alguns autores atribuem esse comportamento à ausência de inervação vagal associada à um atraso humoral na liberação de catecolaminas, fazendo com que mais tempo seja necessário para recuperação da FC conforme as catecolaminas plasmáticas são metabolizadas.[73,75] O comprometimento cronotrópico observado ressalta a importância de prolongados períodos de aquecimento e volta à calma nas sessões de treinamento nessa população.[8] Ademais, alguns autores verificaram que disfunção diastólica pode estar presente nesse grupo de pacientes, evidenciada através de reduzido volume diastólico final, aumento nas pressões de enchimento ventricular e na pressão capilar pulmonar, o que por sua vez, é fator limitante ao mecanismo compensatório de Frank-Starling.[71,76-78] Os mecanismos responsáveis pela disfunção diastólica ainda são incertos, podendo estar associada a disfunção autonômica decorrente da denervação cardíaca, sendo a isquemia relacionada a DVE outro possível fator causal.[6,79]

Evidências demonstram que a reinervação autonômica do coração transplantado é possível. Trata-se de um processo parcial, variável e dependente do tempo, o qual ocorre em 40 a 70% dos pacientes.[73 ,80-83] Entre os primeiros 6 a 12 meses pós-TxC, observa-se denervação cardíaca completa. Contudo, principalmente a partir de dois anos do procedimento, muitos receptores podem apresentar sinais de reinervação simpática e parassimpática. O processo é progressivo, de longo prazo e parece heterogêneo entre os pacientes, podendo envolver o músculo cardíaco, nó sinusal e vasos coronários.[84] Ademais, a

restauração de fibras parassimpáticas difere conforme a técnica cirúrgica, sendo mais frequente nos pacientes submetidos à técnica bicaval em relação a clássica.[83] Bengel et al. estudaram tanto as adaptações anatômicas quanto potenciais repercussões funcionais deste fenômeno. Os autores verificaram que pacientes pós-TxC com reinervação de fibras simpáticas apresentam melhores respostas funcionais. Observou-se maior FC pico, fração de ejeção e tolerância ao exercício nestes indivíduos em comparação ao grupo denervado.[85]

Inúmeras alterações pulmonares estão presentes em indivíduos com IC. Padrões restritivos e obstrutivos estão relacionados a um pior prognóstico,[86] enquanto a reduzida força muscular inspiratória e difusão-alvéolo capilar prejudicada são componentes típicos do quadro de intolerância ao exercício.[48] Em alguns estudos de coorte em que pacientes com IC foram avaliados antes e após o TxC, observou-se melhora na capacidade vital forçada, volume expiratório forçado em um segundo e pressão capilar pulmonar, no entanto sem apresentar diferença na relação volume expiratório forçado em um segundo/capacidade vital forçada, principal marcador de padrão obstrutivo. Estes achados sugerem que ao menos a fisiologia pulmonar restritiva, possa ser em parte atribuída às alterações inerentes ao processo da IC, podendo ser revertida com o TxC.[87-90] Em estudo observacional de Fernandes et al., verificou-se força muscular inspiratória e expiratória máximas superiores seis meses após o TxC em relação ao período de IC prévia. Ademais, os níveis de força respiratória verificados entre 1,5 e 3 anos pós-TxC foram similares aos de indivíduos controles saudáveis.[91] Em contrapartida, prejuízo na difusão alvéolo-capilar permanece após o TxC e está associado ao VO_2 pico atenuado nestes indivíduos.[92,93] As causas precisas para esse comprometimento ainda não foram completamente esclarecidas. No entanto, é possível que seja atribuído à dano na membrana alvéolo-capilar, provavelmente oriunda a lesões microvasculares, que por sua vez, podem ser atribuídos a IC prévia e até mesmo progressivamente agravados pela utilização de imunossupressores.[89,90,94]

Os benefícios do TxC nesse grupo selecionado de pacientes com IC avançada ultrapassam o reestabelecimento da hemodinâmica cardíaca, repercutindo positivamente em outros sistemas fisiológicos. Embora as melhoras observadas sejam de extrema relevância, ocorrem somente de forma parcial, o que faz com que a maioria dos indivíduos pós-TxC apresentem tolerância ao exercício inferior ao observado nos pares saudáveis. Estratégias eficazes em reverter as alterações fisiopatológicas, bem como prevenir os efeitos adversos

advindos da terapia imunossupressora, podem contribuir para o melhor desempenho nas atividades de vida diária, maior capacidade funcional e quiçá menor morbimortalidade nessa população. Neste cenário, o TF desponta como estratégia multifatorial, sendo capaz de favorecer um prognóstico ainda mais favorável.

Exercício físico pós-transplante cardíaco: avaliações e cuidados necessários

A evolução clínica frente ao procedimento, assim como o período de internação é variável entre os pacientes pós-TxC, podendo ser prolongado por meses em alguns casos.[95,96] Atenção especial deve ser direcionada para prevenção de possíveis prejuízos, principalmente musculares e pulmonares, decorrentes da imobilização prolongada. Neste ínterim, a fisioterapia intra-hospitalar, intervenção com eficácia estabelecida na recuperação de outras cirurgias cardíacas,[97,98] é aplicada em alguns centros de referência no pós-TxC. A literatura ainda é escassa sobre o tema e as evidências disponíveis sugerem que a intervenção tende a ser segura e auxiliar na recuperação funcional destes pacientes,[99-101] sendo recomendada em posicionamento mais recente da *European Association of Preventive Cardiology* sobre RCV.[13] De acordo com a experiência do nosso centro de pesquisa (dados não publicados), observamos que os pacientes que recebem a fisioterapia intra-hospitalar e são orientados para manutenção dos exercícios após a alta, muitas vezes retornam para reabilitação ambulatorial (fase 2) com os novos hábitos de exercício preservados e com habilidades adquiridas, o que favorece a progressão na RCV.

No subgrupo de pacientes com TxC recente é necessário cuidado quanto aos possíveis desconfortos decorrentes da toracotomia e um plano de exercícios progressivo que preserve o processo de cicatrização do esterno, especialmente nos primeiros três meses após o procedimento.[101,102] Os profissionais responsáveis pela prescrição e orientação dos exercícios devem atentar para possíveis sinais de rejeição, como redução na tolerância ao exercício, dispneia, edema, arritmias e elevação na temperatura corporal.[9] Portanto, além das mensurações sistemáticas da pressão arterial, FC e glicemia (nos casos necessários) realizadas antes e após as sessões de exercício, é plausível integrar ao registro a avaliação da temperatura e massa corporal, bem como o relato de manifestação de sintomas. Assim, é

possível estabelecer parâmetros individuais e identificar alterações associadas a rejeição, infecção ou outras complicações. Durante episódios de rejeição aguda, em qualquer fase pós-TxC, a intensidade dos exercícios deve ser reduzida. Nos casos severos e/ou com necessidade de pulsoterapia com corticóide o treinamento deve ser interrompido até que haja completa recuperação.[101]

Quanto mais recente a cirurgia, maior a frequência de biópsias.[2] Tendo em vista que este é um procedimento invasivo e que demanda de grande empenho do paciente, é relevante considerar o manejo da sessão de treinamento para outro dia. A apresentação clínica de isquemia em pacientes com DVE pode ser identificada através de sintomas inespecíficos de fadiga, náusea e/ou desconforto abdominal,[2] assim como aqueles mais específicos da IC, como fraqueza, dispneia e palpitações.[103] No entanto, cabe ressaltar que alguns pacientes não manifestam sequer qualquer sintoma.[58] Portanto, a monitorização do enxerto através de exames periódicos é fundamental, tendo em vista o mau prognóstico associado à doença, [104] assim como o potencial risco de o exercício físico ser um gatilho para eventos cardíacos adversos em pacientes com DVE avançada desconhecida.

A avaliação pré-participação do exercício, principalmente na fase ambulatorial, é primordial. Possibilita a adequada estratificação de risco, determinação de cuidados pertinentes a cada caso e prescrição individualizada do treinamento. Em pacientes pós-TxC ela é idealmente ~~é~~ composta por anamnese, exame físico, eletrocardiograma de repouso de 12 derivações, radiografia de tórax, ecocardiograma Doppler com mapeamento de fluxo em cores e teste de exercício, sendo o TCPE o exame padrão ouro para avaliação da capacidade funcional.[7,13] Se este não estiver disponível, um Teste Ergométrico ou Teste de Caminhada de 6 minutos pode ser realizado, sendo de grande valia.[11,105]

A função cronotrópica prejudicada, devido à ausência de inervação cardíaca especialmente nos pacientes recentemente transplantados, impossibilita o estabelecimento de zonas alvo e controle da intensidade do exercício através da FC.[84] Sendo assim, a principal estratégia adotada será o controle da intensidade através da percepção subjetiva de esforço com a Escala de BORG.[11] Através da experiência no nosso centro de pesquisa, observamos que tendo disponível um TCPE recente, a prescrição do exercício aeróbico pode ser baseada na sobrecarga (velocidade e inclinação) atingida nos limiares ventilatórios ou nos percentuais estabelecidos do $\dot{V}O_2$ pico. Por fim, também observamos presença de limitações

osteomioarticulares em muitos pacientes, o que aponta para a necessidade de uma avalição específica dessas condições. Assim, com a colaboração de uma equipe multidisciplinar é possível estabelecer tratamentos concomitantes que possam ser necessários, bem como direcionar as melhores estratégias de exercício.

Reabilitação cardiovascular com ênfase em treinamento físico pós-transplante cardíaco: principais recomendações

Por muito tempo se acreditou que após um evento ou procedimento cardiovascular os pacientes deveriam permanecer acamados por semanas. Considerava-se necessário um período de pelo menos 6 a 8 semanas de repouso absoluto para que houvesse reestabelecimento do quadro, sendo o retorno às atividades cotidianas realizado mediante a muitas limitações. Na ausência de conhecimento científico sobre a interação atividade física e doenças cardiovasculares, os pacientes eram orientados até mesmo ao afastamento das atividades laborais.[106] O que não se sabia na época, é que além do possível sentimento de invalidez com reflexo na vida familiar e social,[106] os pacientes eram privados de inúmeros benefícios clínicos oriundos da mobilização precoce e do TF, atualmente consolidados na literatura científica.[13,21]

Entre as décadas de 60 e 70, surgem os primeiros Centros de RCV no Brasil e os resultados obtidos nestes programas são expostos à comunidade acadêmica. A partir destes feitos, acontecem os primeiros simpósios com especialistas e o interesse sobre assunto aumenta de forma expressiva.[106] Inicialmente direcionadas à doença arterial coronariana, o arsenal contemporâneo de evidências científicas demonstra a segurança e eficácia do TF na promoção da saúde cardiovascular nas diferentes doenças e condições clínicas, incluindo a IC e o pós-TxC.[10-14,21]

Posicionamentos e Diretrizes das principais associações de cardiologia do Brasil e do mundo estão disponíveis e são periodicamente atualizadas.[10-14,106] Definem a RCV como o conjunto de estratégias multidisciplinares integradas e direcionadas para promoção da saúde integral dos indivíduos, entre as quais o TF é componente primordial. Os principais objetivos do TF neste contexto são: (a) auxiliar no controle dos fatores de risco cardiovasculares; (b)

aumentar a capacidade funcional; (c) melhorar diferentes componentes do condicionamento físico; (d) promover qualidade de vida; (e) favorecer um melhor prognóstico. De forma convencional, os programas estruturam-se em quatro fases, cada uma com objetivos e recomendações específicas que acompanham o transcurso da evolução clínica após evento e/ou procedimento cardiovascular. Por definição, a fase 1 ocorre ainda durante o período de internação hospitalar, enquanto as fases seguintes (2, 3 e 4) assumem perfil ambulatorial e podem ocorrer em hospitais, centros especializados em reabilitação, academias e até mesmo através de supervisão à distância no formato "*home-based*", conforme fase da RCV e condições clínicas do participante.[12]

Os principais documentos disponíveis orientam a combinação de treinamento aeróbico e treinamento resistido (TR)[10,12,105,106] para reverter a fisiopatologia prévia ao transplante, reduzir o risco cardiovascular inerente à terapia imunossupressora e promover desfechos clínicos relevantes (classe de recomendação 1 e nível de evidência B).[10] De forma geral, recomenda-se que na fase 2 da RCV, o exercício aeróbico seja iniciado na segunda ou terceira semana pós-TxC com inserção dos exercícios resistidos entre a sexta e oitava semana após o procedimento.[13] Em Diretriz Europeia publicada recentemente considera-se até 3 meses para o início dos exercícios resistidos de membros superiores.[10] Compreende-se a necessidade de maior cautela para realização dos exercícios resistidos de membros superiores, tendo em vista o processo de cicatrização do esterno. Ademais, uma avaliação mais aprofundada através do TCPE será possível na quarta semana após a cirurgia e auxiliará na elaboração da prescrição do treinamento aeróbico.[13] Contudo, é válido considerar que em alguns casos, principalmente naqueles com evolução clínica favorável e realização de RCV fase 1, a continuidade dos exercícios imediatamente após a alta hospitalar pode ser benéfica e prevenir um possível destreinamento. Ainda não há relatos na literatura sobre um programa de TF que integre as fases 1 e 2 da RCV em pacientes pós-TxC.

Parece consenso entre os documentos disponíveis a realização mínima de 30 minutos por sessão de exercício a ser realizada até cinco vezes por semana.[10-13,106] Baseado na prescrição de exercício utilizada nos ECRs e no conhecimento sobre a teoria do TF, o nosso Grupo de Pesquisa em Cardiologia do Exercício (CardioEx) elaborou uma periodização de treinamento que especifica características fundamentais, como frequência, intensidade, duração e tipo dos exercícios que compõem cada microciclo do nosso programa de treinamento, disponível em

publicação prévia.[102] O respectivo projeto de pesquisa está em andamento e os resultados analisados até o momento foram apresentados em Málaga, no Congresso Científico da *European Association of Preventive Cardiology* de 2020.

Estado da arte sobre treinamento físico pós-transplante cardíaco: resultados de ensaios clínicos randomizados e revisões sistemáticas com meta-análise

A capacidade funcional dos pacientes pós-TxC, medida de forma objetiva pelo VO_2 pico, é aproximadamente 50% do observado nos pares saudáveis de mesma idade e sexo.[36,40,108] Embora esse valor já reflita a melhora expressiva de aproximadamente 43% que ocorre no primeiro ano após o procedimento, na ausência de intervenções direcionadas, é muito provável que a capacidade funcional permaneça abaixo do predito nos anos subsequentes sem qualquer melhora adicional.[40,108]

Evidências da década de 90 foram algumas das pioneiras em demonstrar a influência do TF na melhora da capacidade funcional em indivíduos pós-TxC. Richard et al. verificaram valores de VO_2 pico e FC pico próximos ao predito e superiores em indivíduos treinados para *endurance* em comparação aos observados em pacientes que não praticavam exercício regularmente, havendo superioridade também na variável pulso de oxigênio (pulso de O_2).[109] No mesmo período, visando compreender os potenciais benefícios clínicos do exercício realizado de forma sistemática nesta população, os primeiros ensaios clínicos sobre o tema foram desenvolvidos.[17,20]

Kobashigawa et al. randomizaram pacientes recentemente transplantados (até duas semanas do procedimento) para grupo treinamento combinado (TC) ou grupo controle com cuidados usuais. O grupo treinamento realizou durante seis meses três sessões semanais de exercício, compreendendo pelo menos 30 minutos de exercício aeróbico em esteira ou bicicleta e exercícios individualizados de força, ao passo que o grupo controle somente recebeu orientações por escrito sobre exercícios físicos. Neste grupo de indivíduos em que se espera melhora espontânea na capacidade funcional no primeiro ano após a cirurgia, aqueles submetidos ao TF apresentaram aumento superior no VO_2 pico. Além disso, o TF foi eficaz em

promover redução na relação VE/VCO_2 *slope* e aumento na força muscular de membros inferiores avaliada pelo teste de sentar e levantar em um minuto.[20]

Os estudos de Braith et al. também são clássicos da literatura sobre o tema e investigaram especialmente o potencial do TR em reverter as consequências advindas da terapia com glicorticóides sobre a composição corporal e força muscular esquelética. Para isso, randomizaram pacientes para um grupo TR (3 sessões semanais durante seis meses) e outro controle sem exercício. Os indivíduos foram avaliados por *Dual-energy X-ray absorptiometry* e teste de uma repetição máxima antes e 2 meses após a cirurgia, assim como 3 e 6 meses após seguimento de intervenção com exercício ou cuidados usuais. Após dois meses do TxC, ambos os grupos apresentaram aumento na massa gorda, redução na massa livre de gordura e piora nos níveis de força muscular periférica. No entanto, seis meses após o TxC, os pacientes alocados para o treinamento apresentam massa livre de gordura superior ao observado antes da cirurgia, enquanto o grupo controle apresentou piora progressiva neste parâmetro. O mesmo comportamento, porém, na direção inversa, foi verificado em relação a massa gorda. Além disso, apesar de os dois grupos apresentarem melhora na força muscular no transcorrer do tempo, o aumento foi pelo menos quatro vezes superior no grupo treinado.[17] Em outra publicação, o grupo de pesquisadores demonstrou que o mesmo programa de treinamento foi eficaz em aumentar a densidade mineral óssea, enquanto o grupo controle permaneceu com os índices reduzidos pelo menos até seis meses do transplante.[110]

Demonstrado o potencial terapêutico e a boa tolerabilidade dos pacientes ao TF, número crescente de ECRs foram desenvolvidos. O acúmulo de evidências possibilitou a sumarização dos achados através de uma revisão sistemática com meta-análise desenvolvida pela Cochrane em 2017.[21] Neste estudo, foram incluídos 10 ECRs envolvendo ao todo 300 indivíduos com idade média de 54 anos e maioria do sexo masculino. Entre os estudos, nove compararam alguma modalidade de TF, sendo a maioria com treinamento aeróbico, a um grupo controle sem exercício. Os autores também incluíram um ECR cruzado que comparou o treinamento intervalado de alta intensidade (TIAI) ao treinamento contínuo moderado (TCM).[103] Devido à natureza das comparações, os resultados deste estudo foram apresentados de forma isolada, enquanto os demais foram meta-analisados. Com moderada certeza na evidência avaliada através dos critérios GRADE, o principal achado do estudo foi que o TF

promove em média um aumento de 2,49 ml.kg^{-1}.min^{-1} (IC 95% 1,63 a 3,36, ml.kg^{-1}.min^{-1}) no VO_2 pico em pacientes pós-TxC. A estimativa de efeito verificada pode ter grande relevância clínica, tendo em vista a associação inversa entre VO_2 pico e mortalidade já bem estabelecida na literatura em diferentes populações.[111] Estudos demonstram que para cada aumento de 1 ml.kg^{-1}.min^{-1} há redução de 10% no risco de mortalidade em indivíduos com doenças cardiovasculares.[112] Apesar de menos estudado o potencial prognóstico no pós-TxC, evidência disponível demonstra o VO_2 pico como forte preditor de sobrevida também nesta população.[113]

São inúmeras as modalidades possíveis de TF. As predominantemente estudadas no contexto da RCV pós-TxC são as seguintes: (a) treinamento aeróbico contínuo moderado ou intervalado em alta intensidade (TCM ou TIAI), geralmente realizados em esteira ou bicicleta ergométrica; (b) TR, utilizando o peso corporal e/ou carga externa; (c) TC, associando exercícios aeróbicos aos de força em um mesmo programa de exercícios. Os resultados observados nos estudos individualmente indicam eficácia e segurança das diferentes estratégias. Contudo, visando conduzir a melhor prática baseada em evidências é necessário conhecer se há diferença entre os efeitos advindos das diferentes modalidades sobre a capacidade funcional, assim como para outros desfechos relevantes nesta população. Ademais, considerando-se os estudos fisiológicos, é plausível que as adaptações ao treinamento possam diferir entre os pacientes recentemente transplantados em comparação aos que realizaram o procedimento a mais tempo.[6]

No que tange aos exercícios aeróbicos, alguns estudos investigaram as possíveis diferenças nas adaptações entre o TIAI e o treinamento contínuo moderado TCM.[115-118] Em pacientes em média seis anos pós-TxC, Dall et al. verificaram que o TIAI foi mais eficaz que o TCM em aumentar o VO_2 pico (4,9±2,7 *versus* 2,6±2,2 ml.kg^{-1}.min^{-1}) e na resposta cronotrópica sobre a FC pico e FC de reserva. O grupo TIAI também apresentou redução na FC de repouso e melhora na FC de recuperação, sem haver diferença estatística entre os grupos.[115] A melhora nos parâmetros de FC são desejáveis, tendo em vista que a FC pico reduzida está entre os fatores que limitam a capacidade funcional nestes indivíduos,[119,120] ao mesmo tempo em que uma FC de recuperação atenuada é um preditor independente de mortalidade em pacientes com IC.[121] Melhoras promovidas pelo TF sobre a função cronotrópica podem representar

resposta autonômica mais eficiente nestes pacientes, quiçá promovidas pela facilitação do processo de reinervação cardíaca, o que por sua vez, carece de investigações específicas.

A tolerabilidade e eficácia do TIAI ainda não havia sido estudada em pacientes recentemente transplantados. Neste grupo de indivíduos com ajuste limitado da FC durante exercício, não se conhecia a resposta frente a um protocolo que alterna blocos de alta intensidade com intervalos de recuperação em intensidade inferior, consequentemente requerendo ajustes fisiológicos sistemáticos e eficientes. Recentemente Nytroen et al.[117,118] randomizaram pacientes em média 11 semanas pós-TxC para 9 meses de TIAI (4x2-4min, 16-18 Borg; 3x3min, 11-13 Borg) ou TCM (12-15 Borg). O TIAI foi periodizado, ambos os grupos realizaram de 2 a 3 sessões de exercícios por semana e pelo menos em algum momento do treinamento realizaram exercícios de força. Corroborando com os achados de Dall et al.,[115] ambos os grupos promoveram melhora no VO_2 pico, sendo o aumento superior no grupo TIAI, diferença de 1,8 $ml.kg^{-1}.min^{-1}$ (IC 95% 0.1 a 3.5) entre os grupos. O TIAI também promoveu aumento superior na resistência muscular de membros inferiores, sem haver diferença entre os grupos na melhora observada da força deste mesmo seguimento. Ademais, os dois grupos apresentam melhora na relação VE/VCO_2 *slope*, FC pico, FC de recuperação, índice cronotrópico e no escore de componente físico do SF-36. Em relação a outros desfechos secundários, observou-se melhora no pulso de O_2 e a Dif a-v O2 somente no TIAI, ao mesmo tempo em que apenas neste grupo se verificou piora na função endotelial, aumento na pressão arterial sistólica e no percentual de gordura corporal.[107]

Outros desfechos relacionados a fisiopatologia peculiar à condição pós-TxC foram avaliados em estudos que compararam o TIAI aos cuidados usuais. Nytroen et al. investigaram o potencial do exercício físico na prevenção da DVE em pacientes em média quatro anos após o TxC.[122] Verificou-se após um ano de seguimento, progressão atenuada dos volumes total e percentual de ateroma avaliados por ultrassom intravascular nos pacientes que realizaram treinamento em comparação ao grupo controle, fortalecendo a hipótese dos autores. Variável interessante neste contexto é a espessura íntima máxima. Em estudo de coorte foi demonstrado que um aumento de ≥0,5 mm no primeiro ano pós-TxC é marcador prognóstico de evolução desfavorável de DVE em cinco anos, representado pela maior incidência de morte, falência do enxerto e eventos cardiovasculares adversos.[123] No estudo de Nytroen et al., houve uma tendência à diferença do delta da espessura íntima máxima entre os grupos

(p=0,054) e somente o grupo controle apresentou aumento nesta variável.[122] Cabe considerar que o aumento observado foi de 0,05 mm, bem inferior aos valores associados a pior prognóstico do estudo de Kobashgawa et al.[123] Contudo, permanece plausível especular o efeito do TF na prevenção da DVE, provavelmente de maior magnitude sobre os casos mais predispostos à doença e iniciando em bases mais precoces após a cirurgia.

Demais achados do estudo de Nytroen et al. se referem a eficácia do TIAI em melhorar a capacidade funcional (3,6 $ml.kg^{-1}.min^{-1}$, IC 95% 2,0 a 5,2) concomitante ao aumento na força e resistência de membros inferiores. Além disso, o grupo treinamento apresentou aumento na FC pico, FC de reserva, índice cronotrópico e pressão arterial sistólica no pico do esforço. Observou-se discreta diferença na FC de repouso entre os grupos e nenhuma diferença na FC de recuperação e pressão arterial em repouso. Somente o grupo treinamento apresentou aumento no pulso de O_2. Não se observou diferença na relação VE/VCO_2 *slope*.[111] Em estudo sobre a mesma modalidade de treinamento de Hermann et al,[124] o TIAI além de eficaz em aumentar o VO_2 pico, melhorou a função endotelial e reduziu a pressão arterial sistólica, fatores que estão associados ao desenvolvimento da DVE e hipertensão arterial, por sua vez altamente prevalente nesta população.[28] Observou-se melhora no escore de saúde mental do questionário SF-36 e nenhuma diferença foi observada na FC de repouso e FC pico.[125,126] Os pesquisadores também avaliaram o efeito do exercício em parâmetros ecocardiográficos de pressões de enchimento ventricular. Em pacientes em média 6 anos pós-TxC com ausência ou leve disfunção diastólica que realizaram oito semanas de TIAI três vezes por semana, nenhuma alteração nas relações E/e' e E/A, assim como no tempo de desaceleração foi observada.[126]

Até o momento, a eficácia do TR realizado de forma isolada foi avaliada somente nos estudos de Braith et al.[17,53,110] No entanto, considerando-se a relevância da especificidade para essa população, além de Kobashigawa et al.,[20] outros grupos de pesquisa consideraram a inclusão de exercícios de força em protocolos de TC. Haykowsky et al.,[127] após 12 semanas de treinamento aeróbico combinado à resistido, verificaram aumento no VO_2 pico (3,11 $ml.kg^{-1}.min^{-1}$, IC 95% 1.2 a 5) e massa magra, acompanhado de melhora expressiva na força de membros superiores e inferiores e tendência de aumento na FC pico, sem melhora na função sistólica ventricular e função endotelial em pacientes em média 5,4±4,9 anos pós-TxC. Wu et al.[128] ao avaliaram a eficácia de oito semanas de TC no perfil *home-based*, observaram melhora no domínio físico da qualidade de vida e na força e resistência muscular avaliadas

pelo teste de sentar e levantar em um minuto e índice de fadiga, respectivamente. No entanto, não se observou aumento no VO_2 pico, assim como nenhuma alteração em variáveis cronotrópicas, como FC de repouso e FC pico.

O treinamento *home-based* é estratégia atrativa, já que pode ser acessível há muitos pacientes que não teriam condições de manter as sessões presenciais. Visando conhecer se há diferença na eficácia entre o treinamento à distância e o modelo tradicional supervisionado, Karapolat et al. compararam o efeito do TC hospitalar ao mesmo protocolo de exercício realizado em casa.[129,130] Enquanto o treinamento *home-based* somente foi eficaz na melhora do domínio dor no questionário de qualidade de vida, o treinamento em centro de reabilitação promoveu aumento no VO_2 pico (2,8 $ml.kg^{-1}.min^{-1}$), FC de reserva e na maioria dos sub-escores de qualidade e vida do SF-36, exceto para vitalidade e função social. Contudo, não foram observadas melhoras na FC de recuperação e índice cronotrópico.

Conforme estudos de Tegtbur et al. e Bernardi et al.,[131,132] o TCM realizado em base domiciliar é eficaz na melhora do VO_2 pico em 1,3 e 4,68 $ml.kg^{-1}.min^{-1}$, respectivamente. É interessante ressaltar que no estudo de Bernardi et al.[132] que incluiu pacientes seis meses após o TxC, observou-se melhora no controle autonômico da FC e PA através da manobra de sucção de pescoço no grupo que realizou seis meses de treinamento, acompanhada de redução na pressão arterial sistólica e diastólica no repouso. Através destes achados, os autores sugerem que o exercício em bases crônicas possa acelerar o processo de reinervação cardíaca e auxiliar na restauração da sensibilidade barorreflexa. Nenhuma diferença foi verificada na FC de repouso e na eficiência ventilatória mensurada através das relações VE/VO_2 *slope* e VE/VCO_2 *slope*.

A modalidade de TF mais estudada e que segue preconizada no contexto de RCV é o TCM. Braith et al.[133] verificaram que aproximadamente dois meses após a cirurgia, os pacientes apresentaram melhora significativa na função endotelial em relação ao período pré-TxC. A dilatação mediada pelo fluxo foi mantida ao longo de três meses no grupo treinamento, enquanto piorou no grupo controle. O grupo treinado também apresentou redução nos níveis plasmáticos em repouso de norepinefrina, havendo uma tendência ao aumento no grupo controle. Os autores sugerem que este achado possa estar associado ao potencial efeito do exercício em atenuar a hiperatividade simpática causada pela terapia com ciclosporina. Apesar de não ocorrer nenhuma diferença na FC pico, FC de repouso e pressão arterial,[134]

observou-se aumento de 4 $ml.kg^{-1}.min^{-1}$ no VO_2 pico,[133] o que também foi observado no estudo de Pascoalino et al.[135] Neste estudo com prescrição semelhante, porém em pacientes com aproximadamente seis anos de TxC, verificou-se além da melhora na capacidade funcional (2,1 $ml.kg^{-1}.min^{-1}$), redução na pressão arterial sistólica (24 horas e vigília) e diastólica (24 horas, vigília e sono) avaliada por monitorização ambulatorial da pressão arterial. A rigidez arterial também foi avaliada através de velocidade da onda de pulso carotídeo-femoral, sem evidência de mudança com o treinamento. O grupo treinamento foi o único a apresentar aumento na FC pico. Nenhum dos grupos apresentou diferença na FC de repouso, FC de recuperação e relação VE/VCO_2 *slope*.

Em relato posterior, Ciolac et al.[133] demonstraram que o processo de inervação cardíaca, avaliada através das respostas cronotrópicas ao TCPE, podem influenciar nas adaptações cardiorrespiratórias e hemodinâmicas do treinamento. Os pesquisadores compararam indivíduos com e sem evidências funcionais de reinervação cardíaca, ambos submetidos a um programa de TF de doze semanas. O aumento esperado no VO_2 pico foi verificado somente no grupo considerado reinervado, que também apresentou redução na pressão arterial sistólica e diastólica avaliada por monitorização ambulatorial da pressão arterial, enquanto o grupo denervado apenas reduziu a pressão arterial diastólica.

A partir de um corpo de evidências cada vez mais robusto sobre os efeitos do TF em pacientes pós-TxC, torna-se interessante a realização de revisões sistemáticas com meta-análise. A revisão Cochrane, até o momento representa a evidência mais robusta sobre o tema. Em revisão prévia, a partir da literatura disponível até o ano de 2011, Hsieh et al.[134] concluíram que o treinamento físico é eficaz no aumento do VO_2 pico e força muscular. É necessário atentar para o pequeno número de estudos elegíveis para as análises naquele momento, com somente dois estudos meta-analisados para o desfecho força muscular.

Algumas revisões sistemáticas com meta-análise exploraram os efeitos do TIAI.[135,136] Perrier-Melo et al.[135] em 2018, concluíram que 8 a 12 semanas de TIAI são suficientes para aumentar o VO_2 pico e FC pico em indivíduos pós-TxC. Cabe destacar que entre os três estudos incluídos na análise de VO_2 pico e dois elegíveis para de FC pico, um destes é o de Haykowsky,[120] no qual as sessões de TIAI foram iniciadas somente no último mês de treinamento e alternadas com sessões de TCM e treino resistido, configurando-se predominantemente como TC. A mesma consideração pode ser feita sobre a revisão recente

de Conceição et al.[136] que também incluiu nas análises de TIAI *versus* cuidados usuais o estudo com TC. Os resultados para variável VO_2 pico e FC pico vão na mesma direção do observado na revisão de Perrier-Melo.[135] Cabe salientar que apesar do conjunto de evidências ser a mesma, as estimativas de efeito e respectivos IC 95% são diferentes. Entre as informações relatadas que nos permitem a comparação sobre o método adotado em cada estudo, verifica-se que uma optou pelo modelo de efeito fixo, enquanto a outra o modelo de efeitos randômicos. Contudo, não há evidências de heterogeneidade em nenhuma das meta-análises ($p>0,05$, I^2 0%). Outra diferença que pode ser observada e responsável pelas diferenças, é que um estudo relata utilização das diferenças de deltas, enquanto no outro, aparentemente foi utilizado a comparação dos valores pós-seguimento em cada grupo. Na revisão de Conceição et al.[136] também foi realizada a comparação entre TIAI e TCM, e a partir da meta-análise de dois estudos, verificou-se que em média os pacientes que realizam TIAI apresentam aumento superior no VO_2 pico e FC pico em relação aos submetidos ao TCM.

Recentemente Souza et al.[137] sumarizaram o efeito do treinamento aeróbico na função endotelial em pacientes pós-TxC. Apesar da estimativa de efeito indicar o possível benefício do treinamento na melhora da dilatação mediada pelo fluxo, o IC 95% cruza discretamente a linha da nulidade, acompanhado de alta heterogeneidade ($p=0,007$, I^2 80%), permanecendo incerta a eficácia do TF em promover melhora na função endotelial nesta população.

Na revisão Cochrane que evidenciou a eficácia do TF na melhora da capacidade funcional, os autores também pretendiam avaliar a eficácia sobre a qualidade de vida relacionada à saúde. A meta-análise sobre este desfecho não foi possível devido aos diferentes instrumentos utilizados entre os estudos. A partir de análise descritiva, os autores afirmam que não parece haver benefício do TF sobre a qualidade de vida relacionada à saúde, ao menos quando avaliada pelos questionários genéricos. Em relação à desfechos de segurança, entre os estudos incluídos, foi relatado somente um evento adverso (infarto agudo do miocárdio resultando em IC) no grupo controle no estudo de Nytroen et al.[111] sem nenhum evento ocorrido no grupo intervenção.[21]

O conjunto de evidências torna inequívoca a eficácia do TF sobre a capacidade funcional em indivíduos pós-TxC.[21] A partir da estratégia, também se observa aumento na força e resistência muscular esquelética em todos os ECRs que avaliaram este desfecho. A maioria dos estudos demonstra que o exercício sistemático é capaz de aumentar a FC pico e

a FC de reserva. Contudo, os resultados sobre a FC de repouso e FC de recuperação são divergentes entre os experimentos. Também não é claro o efeito do treinamento sobre a função endotelial, porém, o benefício é muito provável. Em estudo pioneiro,[17] TF resulta em melhora expressiva na composição corporal, o que é apoiado por algumas evidências e por outras não. Os resultados observados sobre as repostas pressóricas são favoráveis, enquanto o efeito sobre a qualidade de vida relacionada à saúde permanece incerto, havendo achados mais consistentes sobre o benefício no componente de saúde física. Menos se conhece sobre o efeito do TF sobre variáveis prognósticas obtidas pelo TCPE, como VE/VCO_2 *slope* e pulso de O_2.

JUSTIFICATIVA E OBJETIVOS

As evidências sugerem benefícios multifatoriais do TF em pacientes pós-TxC, melhorando a capacidade funcional e repercutindo positivamente em diferentes respostas fisiológicas que podem auxiliar no controle dos fatores de risco cardiovasculares e atenuar os efeitos adversos da terapia imunossupressora. Da mesma maneira, é possível que as adaptações crônicas ao exercício físico possam contribuir na preservação do enxerto e até mesmo para o melhor prognóstico nesta população, o que é especialmente relevante ao se considerar o potencial do TF em promover aumento na sobrevida a longo prazo. Os ECRs disponíveis investigaram a eficácia de diferentes modalidades de TF sobre o VO_2 pico, qualidade de vida e outras variáveis intermediárias que contribuem para o quadro de intolerância ao exercício e/ou são reconhecidas como marcadores prognósticos em indivíduos com doenças cardiovasculares.

A realização de uma revisão sistemática que considere as diferentes modalidades de TF e os diferentes desfechos clínicos relevantes neste contexto, possibilitará o conhecimento abrangente e aprofundado da literatura sobre o tema. Ademais, a síntese de resultados associado a adequada análise na certeza das evidências poderá gerar nova evidência que oriente as melhores condutas clínicas e/ou aponte os aspectos que carecem de maiores investigações.

Neste sentido, o desenvolvimento de uma revisão sistemática com meta-análise em rede atende de forma mais adequada a esta proposta, uma vez que possibilita a comparação de três ou mais intervenções de exercícios simultaneamente em uma única análise, combinando evidências diretas e indiretas em uma rede de estudos e produzindo uma classificação hierárquica das intervenções. Por fim, é necessário explorar além da segurança, a eficácia das diferentes modalidades de TF sobre desfechos que ainda não foram meta-analisados, considerando também análises sobre os potenciais modificadores de efeito, como o tempo pós-TxC e peculiaridades da prescrição do treinamento.

Objetivos primários

- Comparar a eficácia de diferentes modalidades de treinamento físico (treinamento contínuo moderado, treinamento intervalado de alta intensidade, treinamento resistido e treinamento combinado, considerando *home-based* e *center-based*) na melhora do VO_2 pico em pacientes pós-TxC;

- Comparar a ocorrência de eventos adversos, como vertigem, tontura, queixas musculoesqueléticas, síncope, hipotensão, pressão arterial elevada ou eventos cardiovasculares (angina, arritmias, infarto agudo do miocárdio, acidente vascular encefálico e morte) durante e após sessões de diferentes modalidades de treinamento físico.

Objetivos secundários

- Comparar quantitativamente, através de uma meta-análise por pares (treinamento físico *versus* cuidados usuais) e, se possível, por meio de uma meta-análise em rede, a eficácia do treinamento contínuo moderado, treinamento intervalado de alta intensidade, treinamento resistido e treinamento combinado (*home-based* e *center-based*) em relação às seguintes variáveis: VE/VCO_2 *slope*, *oxygen uptake efficiency*

slope (OUES), FC (repouso, pico e recuperação), pulso de O_2 (VO_2/FC), pressão arterial sistólica e diastólica pico, percepção subjetiva de esforço pico, distância no teste de caminhada de 6 minutos, qualidade de vida relacionada à saúde, função endotelial, força muscular, e percentual de gordura e de massa magra;

- Comparar quantitativamente, através de uma meta-análise por pares (treinamento físico *versus* cuidados usuais), a eficácia e segurança do treinamento físico nos seguintes subgrupos: (a) pacientes pós-TxC recente (<6 meses) *versus* pós-TxC tardio, (b) treinamento físico home-based *versus* center-based e (c) diferentes períodos de intervenção com exercício físico.

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ARTIGOS PUBLICADOS

Os demais artigos publicados relacionados a Tese estão disponíveis nos apêndices deste documento.

Artigo 1. REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE I

Artigo 2. REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE II: TREINAMENTO FÍSICO PÓS-TRANSPLANTE CARDÍACO

Artigo 3. REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE III: RECOMENDAÇÕES PARA TREINAMENTO PÓS-TRANSPLANTE CARDÍACO

Artigo 4. EXERCISE TRAINING MODALITIES FOR HEART TRANSPLANT RECIPIENTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS PROTOCOL

BMJ *(intended publication)*

Exercise Training Modalities for Heart Transplant Recipients:

A Systematic Review and Network Meta-Analysis

Authors and affiliations:

Juliana Beust de Lima, MSc[1,2,4], Douglas dos Santos Soares, MSc[1,4], Filipe Ferrari, MSc[1,2,4], Nelson Carvas Junior, MSc[5], Gabriel Carvalho[2], Santiago Alonso Tobar Leitão, MSc, PhD[1,4], Lívia Adams Goldraich, MSc[3,4], Nadine Clausell, MSc, PhD,[1,3,4,6] and Ricardo Stein, MSc, ScD[1,2,4,6]

[1] Graduate Program in Cardiology and Cardiovascular Sciences, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[2] Exercise Cardiology Research Group, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[3] Heart Failure and Cardiac Transplant Unit, Cardiology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[4] Interdisciplinary Research Group in Translational Cardiology, Clinical Research Center, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[5] Department of Evidence-Based Health, Brazilian Cochrane Center, Universidade Federal de São Paulo, São Paulo, SP - Brazil

[6] Associate Professor, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS – Brazil

Corresponding author

Juliana Beust de Lima, MSc
Serviço de Fisiatria e Reabilitação, Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos, 2350
Porto Alegre, RS 90035-903, Brazil
E-mail: julianabeustdelima@gmail.com

Authors' contributions

Conception of the study: JBL, DSS, FF, SATL, RS

Major drafters of the protocol: JBL, DSS, FF, NCJ, RS

Minor drafters of the protocol: SATL, GC

Provided feedback to the protocol: LAG, NC, RS

Data extraction and synthesis: FF, NCJ, JBL

Assessment of the risk of bias and certainty in the evidence: DSS, SATL, JBL

Major drafters of the manuscript: JBL, RS

Guarantor of the review

Juliana Beust de Lima, MSc

Statement

The protocol of this network meta-analysis was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement and the PRISMA-P 2015 Explanation and Elaboration Document. The same documents and the PRISMA Extension for Network Meta-Analysis of Health Care Interventions were used to prepare this report.

Registration

This systematic review and network meta-analysis was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020191192) and previously published (doi:10.1136/bmjopen-2020-044975).

Funding statement

This protocol was partially supported by the Hospital de Clínicas de Porto Alegre Research Incentive Fund (FIPE-HCPA), Porto Alegre, Brazil – Project number 2018-0292. JBL and GC are Conselho Nacional de Pesquisa e Desenvolvimento (CNPq) grant recipients. DSS and FF are Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) grant recipients.

Role of the sponsor

This study is conducted by an academic institution and a research group that has no relationship with the pharmaceutical industry.

Competing interests

All authors declare that they have no competing interests.

Abbreviations

CPET: cardiopulmonary exercise test; CT: combined training; ET: exercise training; HIIT: high-intensity interval training; HR: heart rate; HTx: heart transplant; MICT: moderate-intensity continuous training; OUES: oxygen uptake efficiency slope; RT: resistance training; VO_2 peak: peak oxygen consumption; V_E/VCO_2 slope: minute ventilation relative to carbon dioxide production; V_E: minute ventilation; VO_2/HR: oxygen pulse; RCT: randomized controlled trial.

ABSTRACT

Objective

To compare the efficacy and safety of different exercise training (ET) modalities in improving peak oxygen consumption (VO_2 peak) and other important secondary outcomes in heart transplant (HTx) recipients.

Design

Systematic review and network meta-analysis.

Eligibility criteria

Randomized controlled trials enrolling adult (HTx) recipients with the presence of at least one ET group, which might be compared with another training modality and/or a usual care/non-exercise control group for a minimum of 4 weeks of intervention.

Outcomes

The primary outcomes were (VO_2 peak) and occurrence of exercise-related adverse events. Secondary outcomes were the interaction between pulmonary ventilation, pulmonary perfusion, and cardiac output, oxygen uptake efficiency slope, heart rate response, oxygen pulse, peak blood pressure, and peak Borg Rating of Perceived Exertion scale. In addition, we evaluated the 6-minute walking distance, health-related quality of life, endothelial function, muscle strength, body fat percentage, and lean mass.

Information sources

We performed a comprehensive literature search in PubMed/MEDLINE, Embase, The Cochrane Library, CINAHL, Scopus, SportDISCUS, Web of Science Core Collection, and PEDro from inception until November 2020. Two registries (ClinicalTrials.gov and REBEC) were also searched for potential results of unpublished studies. There was no restriction on language, date of publication, publication status, or sample size.

Risk of bias within and across studies

Risk of bias was assessed using the Cochrane RoB 2.0 tool, and confidence in the results, through the Confidence in Network Meta-Analysis (CINeMA) tool.

Results

Were identified 3349 records through database searching. After exclusion of duplicates, screening of titles and abstracts (n=2033), and reading full-text articles (n=72), 14 studies (22 publications) were included for quantitative synthesis across all outcomes. Overall, 473 HTx recipients (most male; mean age, 35.6±12.9 to 60.6±2 years) were allocated to any of the treatments considered. On head-to-head comparisons for treatment efficacy, patients who performed CT and HIIT, compared to those allocated to a control group, presented a mean increase of 3.49 (95% CI 1.96 to 5.02) and 4.78 (95% CI 1.88 to 7.69) $mL.kg^{-1}.min^{-1}$ in VO_2 peak, respectively. Both modalities (CT and HIIT) were also associated with a mean increase of 2.14 (95% CI 0.16 to 4.12) and 3.43 (95% CI 0.20 to 6.67) in VO_2 peak, respectively, compared to home-based CT. Furthermore, HIIT was more efficacious than MICT in increasing VO_2 peak (mean difference, 2.08 [95% CI 0.77 to 3.39] $mL.kg^{-1}.min^{-1}$). HIIT and CT are likely the best exercise interventions for this outcome. The certainty of evidence ranged from moderate to very low between comparisons. Limited safety information was reported in 9 (64%) of the eligible studies. No exercise-related adverse events were reported.

Conclusion

Moderate-certainty evidence suggests that CT and HIIT probably increase VO_2 peak at clinically relevant magnitudes and likely are the most efficacious interventions for this outcome, with HIIT probably being superior to MICT in terms of functional capacity improvement in HTx recipients. There is very low certainty evidence that both CT and HIIT may be more efficacious than home-based CT in increasing VO_2 peak. The available evidence suggests that different ET modalities are safe in heart transplant recipients. However, properly designed studies are needed to assess adverse events.

Registration

PROSPERO CRD42020191192

Data sharing

Open Science Framework tool, available at: https://osf.io/3rwxb/

INTRODUCTION

Heart transplantation (HTx) is the treatment of choice for selected patients with end-stage heart failure, representing the pinnacle of available therapy.[1] Although transplantation improves quality of life and increases life expectancy,[2,3] HTx recipients frequently experience impaired functional capacity,[4] in addition to other complications inherent to the use of immunosuppressants.[5] Reduced exercise tolerance, measured by peak oxygen consumption (VO_2 peak), occurs secondary to damage to both the central (cardiac and pulmonary) and peripheral (vascular and skeletal muscle) components.[6]

In this sense, concomitantly with prevention of HTx-related complications and control of cardiac risk factors, a structured rehabilitation program is recommended and may be an adequate strategy to assist in secondary prevention in these patients.[7-9] Evidence suggests a multifactorial beneficial effect of exercise training (ET) in HTx recipients.[6] Small randomized controlled trials (RCT) have shown the potential of exercised-based rehabilitation to improve autonomic control (both cardiac and peripheral),[10] muscle strength, and body composition,[11] while for endothelial function[12] and health-related quality of life,[13] the effect remains unclear. Additionally, in a Cochrane systematic review and meta-analysis, ET was efficacious for increasing VO_2 peak.[13] However, considering the broader spectrum of exercise interventions, it is unknown whether any modality is superior in terms of efficacy or potential for harm. In addition, synthesizing the effect of ET on other clinically relevant outcomes will assist in understanding the therapeutic potential of ET in secondary prevention in this population.

Different ET modalities have been studied in patients after HTx, such as endurance training (moderate-intensity continuous, MICT and high-intensity interval training, HIIT),[13-15] resistance training (RT),[11,16] and the association of both, combined training (CT).[17,18] Indeed, CT is the most recommended modality for cardiovascular rehabilitation, despite the lack of robust evidence of its superiority over other modalities in this specific population.[8,9] In addition, there is little information about the characteristics of ET (e.g., frequency, intensity, volume and type), as well as differences in adaptation depending on whether training is begun early or late after surgery. Even less is known about the true effect of ET on other relevant parameters beyond VO_2 peak in the HTx scenario.

In patients with heart failure, some variables measured by cardiopulmonary exercise testing (CPET), such as VO_2 peak, the ratio of minute ventilation (VE) to carbon dioxide production (VE/VCO_2 slope),[19,20] and heart rate (HR) recovery after ET[21] were identified as

important prognostic markers. However, in HTx, the evidence base is much less clear. In a retrospective study, VO_2 peak and self-reported functional capacity were found to be strong predictors of survival in HTx recipients.[22] In turn, muscle strength and body fat seem to influence exercise capacity.[23] Interestingly, while the main limiting symptom for ET before HTx was dyspnea, after the procedure, patients reported interruption of exercise due to leg fatigue and muscle exhaustion.[4] In addition, another important factor is the chronotropic response to ET[24] due to the involvement of a denervated heart in increasing HR, contributing to the reduction of exercise tolerance and influencing adaptations to ET.[25,26]

In this systematic review and network meta-analysis, we will compare the efficacy and safety different modalities of ET based on VO_2 peak improvement. Furthermore, as secondary objectives, we will quantify the effect of ET on important outcomes that have not yet been scrutinized, while exploring factors that may influence physiological adaptations to ET.

Objectives

Primary objectives

- To compare the efficacy of different ET modalities (MICT, HIIT, RT, and CT – considering both center-based and home-based ET) in improving VO_2 peak in HTx recipients;
- To compare the incidence of exercise-related adverse events, such as vertigo, dizziness, musculoskeletal complaints, syncope, hypotension, elevated blood pressure, or cardiovascular events (angina, arrhythmias, myocardial infarction, stroke and death) during and after sessions of different ET modalities.

Secondary objectives

- To compare quantitatively, through pairwise meta-analysis (ET *versus* usual care) and, if possible, network meta-analysis, the efficacy of MICT, HIIT, RT, and CT (center-based and home-based ET) in regard to the following variables: VE/VCO_2 slope, oxygen uptake efficiency slope (OUES), HR (rest, peak and recovery), peak oxygen pulse (VO_2/HR), peak systolic and diastolic blood pressure, peak Borg Rating of Perceived Exertion score, 6-minute walking distance, health-related quality of life, endothelial function, muscle strength, and fat and lean mass percentage;
- To compare quantitatively, through pairwise meta-analysis (ET *versus* usual care), the efficacy and safety of ET in the following subgroups: patients in the recent (less than 6

months) *versus* late post-HTx period and those receiving center-based *versus* home-based ET, as well as at different follow-up periods (less than 6 months *versus* at least 6 months).

METHODS

Protocol and registration

The protocol of this study was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement[27] and the PRISMA-P 2015 Explanation and Elaboration Document.[28] The same documents, as well as the PRISMA Extension for Network Meta-Analysis of Health Care Interventions,[29] were used to prepare this report (see checklist in **Supplementary Material 1**). In addition, the study was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions version 6.1.[30] This systematic review and network meta-analysis was registered in the International Prospective Register of Systematic Reviews – PROSPERO (CRD42020191192) and previously published.[31] All study materials are shared publicly through the Open Science Framework tool, available at: https://osf.io/3rwxb/.

Eligibility criteria

To define eligibility for this systematic review, the Population, Intervention, Comparator, Outcome, and Setting (PICOS) framework was used.

Participants

(a) HTx recipients aged ≥18 years, regardless of sex and race; (b) Patients receiving immunosuppressive therapy according to the transplant center protocol, who did not experience severe complications or high-grade rejection on cardiac biopsies during the ET period. Studies enrolling heterotopic transplant recipients or multiorgan transplant recipients were excluded.

Interventions

We considered ET as a single strategy or as a component of a comprehensive cardiovascular rehabilitation program (after hospital discharge), considering a minimum intervention period of 4 weeks. Center-based and home-based interventions were also considered for the following modalities: MICT, HIIT, RT, and CT.

Intervention definitions

- MICT: training modality in which an exercise session can be performed continuously for moderate to long periods with moderate intensity and to a moderate sense of fatigue. In cardiovascular rehabilitation programs, MICT is usually performed on a treadmill or cycle ergometer.
- HIIT: repeated bouts of high-intensity, short-duration exercise, separated by brief periods of lower-intensity exercise or pauses, allowing active or passive recovery, respectively. In cardiovascular rehabilitation programs, HIIT is usually performed on a treadmill and cycle ergometer.
- RT: set of exercises that require muscle contraction against an external overload, and may or may not involve articular movement. Can be performed against body weight alone or with dumbbells, barbells, elastic bands, weight machines, and other equipment.
- CT: endurance exercises (continuous or interval) plus resistance exercises in the same session or on alternate days during the same training period.
- Center-based: exercise sessions with face-to-face professional supervision held in a training center, e.g., hospital, health center, cardiovascular rehabilitation service.
- Home-based: exercise sessions carried out by patients individually at home, without face-to-face supervision, but under professional guidance.

Comparators

For network meta-analysis, by the very nature of this study, we compared the eligible interventions among themselves and with a usual care/non-exercise control group. For the pairwise meta-analysis, we compared the interventions with their respective control groups (usual care/non-exercise).

Outcomes

Primary outcomes

VO_2 peak measured through CPET in $L.min^{-1}$ and $mL.kg^{-1}min^{-1}$, whenever available. Exercise-related adverse events through the absolute frequency of occurrences specified in the safety outcomes of this article.

Secondary outcomes

Other CPET variables: VO_2/HR in mL/beat and both slopes, VE/VCO_2 slope and OUES as absolute measures. HR (rest, peak, and recovery) in beats/min, peak systolic and diastolic blood pressure in mmHg, and peak Borg Rating of Perceived Exertion score. Other secondary outcomes: 6-minute walk distance (in meters), health-related quality of life using validated instruments, e.g., the 36-Item Short-Form Health Survey and World Health Organization Quality of Life questionnaire, and endothelial function by absolute (mm) and relative (%) flow-mediated dilation, and reactive hyperemia index. Upper and lower extremity maximal strength in kilograms assessed using one-repetition maximum (1RM) testing or another equivalent method, e.g., isokinetic evaluation (Nm), sit-to-stand movements in 1 min (number of repetitions) and hand grip strength test (kg). Relative (%) and absolute (kg) fat mass and lean mass, preferably measured through dual-energy X-ray absorptiometry or bioelectrical impedance analysis.

Safety outcomes

Occurrence of exercise-related adverse events – such as vertigo, dizziness, musculoskeletal complaints, syncope, hypotension, elevated blood pressure, or cardiovascular events (angina, arrhythmias, myocardial infarction, stroke, and death) – during and after exercise sessions.

Study designs

Only RTCs (parallel-group, crossover, or cluster designs) were included. Crossover trials were considered in their full form only if there is a washout period of at least 4 weeks. No restrictions were imposed on language or date of publication.

Information sources and search

Information sources

For a comprehensive survey of the literature, the following databases were searched from inception to November 2020: PubMed/MEDLINE, Cochrane Library, Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, SportDISCUS, Web of Science Core Collection, and Physiotherapy Evidence Database (PEDro). Two registries (ClinicalTrials.gov and REBEC) were also searched for potential results in unpublished studies. We also reviewed the gray literature through OpenGrey and Google Scholar, also considering repositories of dissertations and theses, conference publications, and preprint repositories and databases. A hand search of the reference lists of included studies was also conducted. Authors were contacted by e-mail when further data or any clarification on the publications were required.

Search strategy

The main electronic search strategy was designed for PubMed/MEDLINE and adapted as appropriate for each of the other databases. Queries were developed using MeSH terms and their synonyms, and Boolean operators (where possible) to improve searches. Keywords and MeSH terms include: “heart transplantation”, “exercise”, “resistance training”, “physical endurance”, and “circuit-based exercise”. Comprehensive search strategies for all the databases that were consulted are included in the **Supplementary Material 2**. The report of literature search is in accordance with the PRISMA extension for searching[32] (see checklist in **Supplementary Material 3**).

Study selection

Data managements and selection process

Data extraction was based on the following steps: (1) In Clarivate Analytics Endnote X9® (2018) reference management software, the reviewer (FF) set up a library to gather all studies retrieved from the aforementioned databases; (2) all duplicates were excluded; (3) titles and abstracts were evaluated by two independent reviewers (FF and JBL) for classification as potentially eligible or non-eligible. Divergences were solved by consensus between reviewers, and, when necessary, a third opinion (RS) was requested; (4) studies classified as potentially eligible were read in full, and discrepancies were solved by the same previous method; (5) the studies excluded in the previous stage were compiled in an Excel worksheet, followed by their respective reasons for exclusion (no design of interest, no population of interest, no intervention of interest, no outcomes of interest, or other).

Data collection process and data items

Data were extracted by two independent reviewers (FF and JBL). Disagreements were solved by consensus, and, when necessary, a third opinion (RS) was requested. The reviewers were not blinded to the authors' names, institutions, or periodicals. Whenever available, the following information was extracted:

- Study characteristic: first author, journal's name, year of publication, conflict of interest, publication type, study design (parallel, crossover, or cluster RCT), washout period (weeks), study period (weeks), country, language of the publication, number of patients randomized, DOI, trial registration number, funding, and potential conflicts of interest;
- Patient baseline characteristics: age, weight, height, body mass index, sex, time since transplantation, immunosuppressant therapy, comorbidities, etiology and duration of heart failure, surgical technique, previous exercise-based rehabilitation (phase 1), and presence of possible additional interventions to training; in addition, outcome assessment methods; equipment used (cycle ergometer or treadmill) and peak respiratory exchange ratio (R peak), when CPET performed;

- Interventions and comparators: training modality, material resources, intended target zone and form of intensity control, session volume, weekly frequency and follow-up period; supervisory level information (center-based or home-based);
- Results: number of participants in each group, pre and post-intervention values, change from baseline values (within and between groups), standard deviations, or other measures of dispersion, and P-values.

Geometry of the network

The forest.netmeta function of the netmeta package version 1.2-1, implemented in R-3.6.2 software, was used to build and present the geometry of different interventions. In the graph, nodes were used to represent the interventions and edges to show direct comparisons between interventions. The size of the nodes was used to represent the number of patients allocated to each treatment, and the thickness of the edges represented the number of studies in each comparison. Besides graphs, we provide quantitative data and narrative interpretation about the geometry of the network.

Risk of bias within individual studies

The risk of bias was assessed using the Cochrane RoB 2.0 tool.[33] Assessment of the studies was performed independently by two reviewers (DSS and ST); any disagreements was resolved by consensus or by discussion with a third researcher (JBL). Evaluation of quality was divided into five items: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Also, the risk of bias was classified into three categories: (1) Low risk of bias; (2) Some concerns; and (3) High risk of bias. Risk-of-bias assessment was performed for each outcome of interest among the eligible studies.

Publication bias

To investigate the influence of small-study effects, we used the funnel plot visual inspection method if at least ten studies were included in a network or pairwise meta-analysis, followed by Egger's test.[34]

Data synthesis

Main analyses

We used difference in means as the principal summary measure of the effect to express comparisons between interventions, combined with the 95% confidence interval (95% CI) as a measure of uncertainty. When the same outcome was presented by different measures, the standardized mean difference was applied. We planned to use the risk ratio (RR) as the summary measure of dichotomous variables. However, the data available on exercise-related adverse events in the studies did not allow use of this measure. When quantitative synthesis was not possible, a systematic narrative synthesis was provided.

For continuous variables, we extracted the mean (or other measure of central tendency) and standard deviation (or other measure of dispersion) of variables at baseline and in the follow-up in each arm of the studies. When available, we obtained the mean change from baseline and standard deviation or other measures of dispersion in each arm of the trials and between studies. For dichotomous outcomes, we collected absolute frequencies in each treatment arm and the information available in the manuscript about this outcome.

Planned methods of analysis

We used the netmeta package version 1.2-1 implemented in R-3.6.2 software for Mac to perform a frequentist network meta-analysis[35] and synthesize direct and indirect evidence of the therapeutic effects of the interventions through a random-effects model. The node-splitting method was used to assess inconsistencies between direct and indirect comparisons when observing a loop connecting three arms. We present a treatment ranking by P-scores based on the point estimates and standard error of the available network. We evaluated transitivity through the distribution of clinical and methodological characteristics (effect modifiers)

between studies in each head-to-head comparison. Furthermore, the statistical manifestation of transitivity, consistency, was considered in the CINeMA tool.[36]

Additional analyses

As previously planned, we performed analyses to compare quantitatively, through pairwise meta-analysis (ET *versus* usual care) via a random-effects model, the efficacy and safety of ET in the following subgroups: patients in the recent (less than 6 months) *versus* late post-HTx period and center-based *versus* and home-based ET, as well as different follow-up periods (less than 6 months and at least 6 months) for subsets of studies. In case of significant heterogeneity or inconsistency, a subgroup analysis was performed to explore, when possible, the following variables: age, sex, and comorbidities. Finally, a sensitivity analysis was performed for the inclusion of studies with high risk of bias and/or missing data.

Risk of bias across studies

We used the CINeMA (Confidence in Network Meta-Analysis) tool[36,37] to assess confidence in the results. The assessments were performed independently by two reviewers (DSS and ST); any disagreements were resolved by consensus or by discussion with a third researcher (JBL). CINeMA considers six domains – within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence – and assigns judgments at three levels (no concerns, some concerns, or major concerns). For each treatment effect, adjudicated levels of confidence corresponding to the usual Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessments of very low, low, moderate, or high were utilized.

RESULTS

Study selection

The database search strategy identified 3349 records. The total number of records identified in each database are available in **Supplementary Material 4**. After exclusion of

duplicates, a total of 2033 titles and abstracts were screened; of these, 72 full-text articles were assessed for eligibility. Across all outcomes, 14 studies (22 publications) were included in quantitative synthesis. The reasons for exclusions and detailed descriptions of each stage of selection are presented in the PRISMA flow diagram (**Figure 1**). On some occasions, different eligible publications reported the same clinical trial registry number, and others reported a similar methodology and results, suggesting that these referred to a single trial. To clarify situations in which the protocol registration number was not found, at least one author of the publication was contacted by email, and the publication classified on the basis of their answer. When the same outcome was presented in two publications from the same study, we considered the outcome data only once in the meta-analysis.

Study characteristics

Among the studies included, 13 are parallel-group RCTs[10,11,15,17,18,38-52] and one is a crossover RCT.[53,54] In 11 of the eligible trials, some ET modality – MICT (n=2), [39,40,48] HIIT (n=2),[45-47,49,50] RT (n=2),[11,38] CT (n=2),[17,18] home-based MICT (n=2), [10,4] or home-based CT (n=1)[44] – was compared to a usual-care control group, while the remaining trials compared two different ET modalities among themselves (MICT *versus* HIIT, n=2; [15,52-54] Center-based CT *versus* Home-based CT, n=1). [41,42] Patient characteristics and outcomes measured in each study and considered in our analyses are shown in **Table 1**. The included studies were published between 1998 and 2020. The initial sample size ranged from 14 to 81 patients, and 473 patients overall were allocated to any of the treatments considered. The samples were predominantly male, and mean age ranged from 35.6 ± 12.9 to 60.6 ± 2 years. Nine studies reported at least the most prevalent heart failure etiology in the sample, and patients were receiving immunosuppressive therapy according to their respective transplant center protocols, as specified in **Supplementary Material 5**. As presented in **Table 2**, the duration of the exercise sessions ranged from ≈28 min. to ≈90 min., with a weekly frequency of 2 to 5 days and a follow-up period of 8 to 48 weeks. Detailed information of exercise prescriptions and control group definitions are presented in the same table, and the co-interventions common to both groups in each study are given in **Supplementary Material 6**. The presentation and summary of network geometry are discussed individually for each possible outcome of the present study. Further information about included studies, such as DOI, registry number, funding, and potential conflicts of interest, is available in **Supplementary Material 7**.

Primary outcomes

Peak oxygen consumption

Network geometry

Twelve studies evaluated VO_2 peak through CPET on a treadmill or bicycle ergometer. According to the geometry of the network graph (**Figure 2**), there are 6 treatments and 12 pairwise comparations that allow 7 direct (designs) and 8 indirect comparisons. The closed loops between (a) control, MICT, and HIIT and (b) control, CT, and home-based CT provides direct, indirect, and mixed estimates for comparisons, as show in **Figure 3**. The lowest frequency of studies (n=1) refers to comparisons of control *versus* CT and CT *versus* home-based CT, while for the other five comparisons, the same number of studies (n=2) was observed.

Risk of bias within studies

The risk of bias assessment for each individual RCT and summary data are presented in **Figure 4**. In the domain "bias due to deviations from intended interventions", nearly all studies were judged to present some concerns (67%) or high risk of bias (33%), representing the domain in which bias was most likely. The highest prevalence (67%) of studies with low risk of bias was only observed in the domain "bias due to missing outcome date". However, the four remaining studies (33%) were judged to be at high risk of bias for the same domain. For "bias in selection of the reported result", 33% of the studies were considered to have low risk of bias, and 67% presented some concerns. For the domain "bias arising from the randomization process", consensus was 42% for low risk of bias, 42% for some concerns, and 16% for high risk of bias; for "bias in measurement of the outcome", the consensus judgment was 33% at low risk of bias, 42% presenting some concerns, and 25% with high risk of bias, respectively. Three studies[39-40] showed a high risk of bias for most domains, while four presented low risk of most biases. [15,48-50,52-54] Regarding the "overall risk of bias", six studies[15,17,1848-50,52-54] were classified as "some concerns", because the trials were judged to raise some concerns in at least one domain without presenting a high risk of bias for any domain. The six remaining studies[10,39-

[47] were classified as having a high overall risk of bias, since this judgment was assigned to at least one of the domains.

Results of individual studies and synthesis of results

The results of individual studies are shown in **Supplementary material 8**. The head-to-head comparisons for treatment efficacy are presented in a league table (**Figure 5**). Patients who underwent CT and HIIT, compared to those allocated to a control group, presented a mean increase of 3.49 (95% CI 1.96 to 5.02) and 4.78 (95% CI 1.88 to 7.69) $mL.kg^{-1}.min^{-1}$ in VO_2 peak, respectively. Both modalities (CT and HIIT) were also associated with an additional mean increase of 2.14 (95% CI 0.16 to 4.12) and 3.43 (95% CI 0.20 to 6.67) in VO_2 peak compared to home-based CT. Furthermore, HIIT was more efficacious than MICT in increasing VO_2 peak, with a mean difference of 2.08 (95% CI 0.77 to 3.39) $mL.kg^{-1}.min^{-1}$. The other exercise training modalities – home-based CT, home-based MICT and MICT – tended to be more efficacious compared to control, since the lower limit of the confidence interval slightly crosses the null line, while the upper limit of the confidence interval reaches clinically relevant values. Thus, the confidence interval includes values that can lead to different clinical conclusions, which indicates at least some concerns about the imprecision of the evidence; such concerns were also present in the other comparisons of training modalities among themselves. According to the prediction interval presented in **Figure 3**, the true HIIT intervention effect to be expected in a future study is in the range of 1.16 to 8.41 $mL.kg^{-1}.min^{-1}$, while the probable effect of CT varies between an increase in 1.57 to 5.40 $mL.kg^{-1}.min^{-1}$ in VO_2 peak. On comparison of HIIT and MICT, the probable effect is between 0.44 and 3.72 $mL.kg^{-1}.min^{-1}$, favoring protocols with higher intensities. In the treatment classification by p-score, HIIT was most likely to be the most efficacious intervention in improving VO_2 peak (0.9205), and all types of exercise training had a higher probability of being more efficacious than control (CT: 0.7146; home-based MICT: 0.5322; MICT: 0.5195; home-based CT: 0.2895; control: 0.0237).

Exploration for inconsistency and risk of bias across studies

The CINeMA tool was used to assess confidence in the network results. The judgments for each treatment comparison in the six domains were made by associating the semiautomatic evaluation with the inspection and analysis of the researchers based on the pre-established CINeMA criteria.[36] Judgments for all CINeMA domains are available in **Figure 6**. To access the "within-study bias" domain, we considered "overall risk of bias" as assessed by RoB V.2.0 and per-study contribution in a matrix. Six comparisons were considered as "some concerns" and nine as "major concerns". "Reporting bias" was undetected for all estimates, because the literature search was very comprehensive and representative. We did not detect evidence of time-lag bias, selective reporting bias, or publication bias, in this case by visual inspection of the funnel plot and Egger's test (p=0.9719). We attribute no concerns about "indirectness" for all comparisons, considering that the included studies fully met the predefined PICOS criteria, and assume transitivity, since we did not observe different distributions in potential effect modifiers between comparisons. In the "imprecision" domain, five comparisons were considered to have "no concerns", three "some concerns", and seven "major concerns", assessed through clinical conclusions drawn from the 95% confidence intervals. The evaluation of heterogeneity by CINeMA considers the agreement between confidence and prediction intervals. For this domain, three comparisons were adjudicated as "some concerns" and the others as "no concerns". There is also no evidence of heterogeneity through statistical tests (overall: Q 1.08, d.f 7, p=0.9934; within designs: Q 0.59, d.f. 5, p=0.9884; between designs: Q 0.49, d.f. 2, p=0.7830). Finally, in the "incoherence" domain, all comparisons were adjudicated as "no concerns", defined by a p-value from SIDE greater than 0.10 for disagreement measures between direct and indirect evidence, as well as a nonsignificant global test on a random-effects design-by-treatment interaction model (X^2 0.489, d.f 2, p=0.783). Visual inspection of incoherence also is possible through the node-splitting mode presented in **Figure 3**; the contribution of direct evidence for each network estimate is available in **Supplementary Material 9**. The CINeMA "confidence rating" ranged from moderate to very low between comparisons. All indirect evidence was judged to be very low. Between direct and mixed evidence, three comparisons were considered very low (home-based CT *versus* control, home-based MICT *versus* control and CT *versus* home-based CT), one as low (MICT *versus* control), and three as moderate (CT *versus* control, HIIT *versus* Control and HIIT *versus* MICT).

Results of additional analysis

Sensitivity analysis was performed considering six studies that presented high risk of bias. Through this sensitivity analysis, network graph remained 4 treatments, 6 pairwise comparisons, 4 direct comparisons and only 1 evidence closed-loop between control, MICT, and HIIT (**Figure 2**). The previously observed effects, such as the superiority of HIIT and CT *versus* control and of HIIT *versus* MICT, remained, as presented in **Figure 5**. There was no evidence of statistical heterogeneity for this evidence network (overall: Q 0.32, d.f 3, p=0.9566; within designs: Q 0.20, d.f. 2, p=0.9052; between designs: Q 0.12, d.f. 1, p=0.7302), and the rank p-scores were as follows: HIIT, 0.8880; CT, 0.6759; MICT, 0.3897; control, 0.0463.

Nine RCTs were included in a pairwise metanalysis comparing any ET modality to a non-exercise/usual care control group. In the pooled analysis, there was evidence of improvement in VO_2 peak in participants undertaking an exercise rehabilitation program compared to those receiving usual care (2.54 $mL.kg^{-1}.min^{-1}$, 95% CI 1.56 to 3.51, p>0.01, prediction interval 1.36 to 3.72; participants = 292; studies = 9). There was no evidence of statistical heterogeneity (I^2 0%; $t^2 = 0$; p = 0.84). Subgroup analyses were conducted to compare the efficacy of ET between patients in the recent (less than 6 months) *versus* late post-HTx period, center-based *versus* home-based ET, as well as different follow-up periods (less than *versus* at least 6 months). There was no significant difference for any of these comparisons: recent (n=2) *versus* late post-HTx period (n=7): 2.89 $mL.kg^{-1}.min^{-1}$ (95% CI -1.28 to 7.07) *versus* 2.52 $mL.kg^{-1}.min^{-1}$ (95% CI 1.51 to 3.52) p=0.09; home-based (n=3) *versus* center-based ET (n=6): 1.71 $mL.kg^{-1}.min^{-1}$ (95% CI 0.36 to 3.60) *versus* 3.44 $mL.kg^{-1}.min^{-1}$ (95% CI 2.03 to 4.85), p=0.08; and less than 6 months (5 studies) *versus* at least 6 months (3 studies) of follow-up: 2.84 $mL.kg^{-1}.min^{-1}$ (95% CI 0.46 to 5.22) *versus* 2.48 $mL.kg^{-1}.min^{-1}$ (95% CI 1.41 to 3.55), p=0.78. There was no evidence of statistical heterogeneity in any subgroup (I^2 0%; $t^2 = 0$; p>0.05), as shown in the **Supplementary Material 10**.

In the pooled analyses for recent HTx recipients, the confidence interval crosses the null line. However, it bears stressing that only two studies with low power were included in this subgroup. Furthermore, the clinical interpretation differed between center-based and home-based ET. With 95% confidence, the true effect estimate of home-based ET is between 0.36 and 3.60 $mL.kg^{-1}.min^{-1}$ in VO_2 peak; for center-based ET, with 95% confidence, the true effect

estimate is between 2.03 and 4.85 $mL.kg^{-1}.min^{-1}$ in VO_2 peak, with the lower limit of the confidence interval above the cutoff for clinical relevance. Either way, the confidence intervals of the subgroups overlap in both analyses.

Adverse events

We planned to compare the occurrence of adverse events during and after exercise sessions of different ET modalities in HTx recipients. However, we observed that safety was not included as an outcome in 13 (93%) of the 14 eligible RCTs. Although some information is available in nine (64%) RCTs, as presented in **Table 3**, the adverse events were not prespecified nor reported in detail. In addition, in some reports, it is unclear whether the information refers only to adverse events related to exercise sessions, and there is no explanation of the methods used to obtain these data (e.g., active monitoring, spontaneous reporting, or both). In a study that compared HIIT *versus* standard care, the authors reported that one patient in the control group experienced a myocardial infarction resulting in heart failure, without any other serious adverse events in any of the groups during the follow-up period and with no incident musculoskeletal injuries in the HIIT group.[49,50] One study, which compared HIIT to MICT, was the only trial to include adverse events as a secondary outcome; the monitoring method is described in a published protocol.[55] In this RCT, there were no serious exercise-related adverse events.[15,52] In two reports, the authors state that ET is or appears to be safe.[10,11] However, they do not state which parameters were used for safety assessment. No study reported adverse events related to exercise in HTx recipients that performed some form of ET. The data available in the literature are not sufficient to perform a quantitative synthesis of evidence nor assess the risk of bias for this outcome.

DISCUSSION

According to the previously registered and published protocol, we performed a comprehensive literature review, without restrictions, about the safety and efficacy of different

ET modalities on VO_2 peak in HTx recipients, guided by the best available methodological statements.[27-30,32] The main results are: (1) Moderate-certainty evidence suggests that CT and HIIT probably increase VO_2 peak (mean 3.49 and 4.78 $mL.kg^{-1}.min^{-1}$, respectively); (2) Moderate-certainty evidence suggests that HIIT is superior to MICT in improving VO_2 peak (mean difference, 2.08 $mL.kg^{-1}.min^{-1}$); (3) Very low-certainty evidence suggests that both CT and HIIT may be more efficacious than home-based CT (mean difference, 2.14 and 3.43 $mL.kg^{-1}.min^{-1}$); (4) Based on low- and very low-certainty evidence, the effect estimates of MICT, home-based CT, and home-based MICT point to a possible positive effect of these interventions on the VO_2 peak. However, the lower limit of the confidence interval slightly crosses the null line; (5) Very low-certainty evidence suggests there may be no difference in clinical effect between CT and HIIT, both of which are efficacious; (6) According to the p-score rank, HIIT is likely to be the most efficacious ET modality in improving VO_2 peak, followed by CT; (7) In the pooled analysis of a pairwise metanalysis, there was evidence of a mean improvement in VO_2 peak of 2.54 $mL.kg^{-1}.min^{-1}$ when comparing any type of ET to usual care, without significant differences between the following subgroup analyses: patients in recent *versus* late post-HTx period, center-based *versus* home-based ET, and different ET follow-up periods (less than *versus* at least 6 months); (8) Nine studies provided limited information on adverse events. Among these, no adverse events associated with exercise sessions of any training modality were reported.

One of the main objectives of cardiovascular rehabilitation programs is to improve VO_2 peak, in view of the association between low levels of cardiorespiratory fitness and high risk of cardiovascular disease, all-cause mortality, and mortality attributable to various cancers.[56] The effect estimates observed for HIIT and CT have substantial clinical relevance. Previous studies have shown that increases of this magnitude (≈1 MET) in exercise capacity are associated with 10-25% improvement in survival.[56,57] In this regard, even the slightest improvements are important. In patients referred for cardiovascular rehabilitation, each 1-$mL.kg^{-1}.min^{-1}$ increase in VO_2 peak is associated with a 10% reduction in cardiac mortality.[58] The dose-response association between VO_2 peak and survival[56] makes it interesting to know the effects of each ET modality and whether any is superior to others. In this sense, considering this outcome alone, HIIT probably has an advantage over MICT, and may be more efficacious than home-based CT. Likewise, more satisfactory results can be obtained with CT performed in a rehabilitation center in comparison to the same protocol performed at home by HTx recipients.

Previous systematic reviews with pairwise meta-analysis have compared HIIT to usual care with VO_2 peak in HTx recipients as the main outcome of interest. Both Conceição et al.[59] and Perrier-Melo et al.[60] considered the intervention used in the Haykowsky et al.[17] study to be HIIT. In this RCT, HIIT sessions (only 8 out of 60 sessions) were initiated in the last month of training and alternated with MICT sessions in combination with RT, which would characterize the intervention as predominantly CT (as classified in our study). In the same review, Conceição et al.[59] compared HIIT to MICT, this being just one of the 15 comparisons performed in this study. The direction and magnitude of the effect was very similar to that observed in our results. In the HIIT *versus* usual care comparison, the difference in means of the network meta-analysis seems to be greater. This can probably be attributed to the different eligible studies and to the contribution of indirect comparisons.

We observed differences in ET prescription even within modalities. Unlike other studies with HIIT, Nytroen et al.[15] included resistance exercises in both the MICT and HIIT groups. Considering that the main differences between the groups was the holding of HIIT or MICT sessions, we used the same classification of modality reported by the authors. This RCT reported detailed and progressive training protocols that were feasible for recent HTx recipients.

Beyond the low certainty in the evidence, contrary to our hypothesis and to the results of individual RCTs, we did not observe any efficacy of MICT on exercise tolerance in HTx recipients. In this context, it is prudent not to infer that a lack of evidence of effect represents an actual lack of effect. As in the home-based modalities, there appears to be a tendency of MICT to lead to improvement; on comparison with control, the lower limit of the confidence interval slightly crosses the null line, while the upper limit of the confidence interval reaches clinically relevant values. It is possible that the imprecision in the observed effects was influenced by two factors: (a) inclusion of RCTs with small sample sizes and (b) wide dispersion of data. Despite randomization, we observed relevant differences in baseline VO_2 peak between groups in some studies. Therefore, we opted for a more conservative approach: analyzing the change from baseline. Since most studies did not provide the respective measure of dispersion, we estimated standard deviations, which results in greater variability, while preserving the true point effect estimates.

The p-score ranking suggests that HIIT is the most efficacious intervention. However, with very low certainty in the evidence, there may be no difference in effect between CT and HIIT. A possible absence of difference in effect between these modalities would be interesting,

suggesting that both are equally efficacious options for improving VO_2 peak in cardiovascular rehabilitation programs for HTx recipients. However, one must consider the effect on other outcomes relevant to health post-HTx, which may be influenced by the specificity of the ET program. For example, it is physiologically plausible that CT would be superior in improving muscle strength,[17,18] while HIIT would more efficacious in improving autonomic control,[53] both of which are associated with exercise intolerance in this population.[23,25] Adaptations in these outcomes may also be different between recent *versus* remote HTx recipients.[6] All these factors are associated with safety, and thus must be considered in the individualized training prescription.

In our pooled estimates of pairwise meta-analysis, there was evidence of an improvement in VO_2 peak when any type of ET was compared with usual care. Although this efficacy was previously demonstrated by Anderson et al.[13] potential effect modifiers had not yet been explored. Therefore, we performed subgroup analyses for patients after recent (less than 6 months) *versus* late (6 months or later) HTx, center-based *versus* home-based ET, as well as different follow-up periods (less than *versus* at least 6 months). There was no significant difference for any of these comparisons. However, the clinical interpretation is different between center-based and home-based ET. Studies with greater power are needed to test the hypothesis that center-based ET is superior to home-based ET in increasing VO_2 peak in HTx recipients. In this context, in our network analysis center-based CT was more efficacious than home-based CT.

To achieve a balanced perspective, we considered two primary outcomes: one of efficacy, based on VO_2 peak, and the other of safety, based on exercise-related adverse events. In general, we observed that little attention is directed to safety outcomes in studies of ET in HTx recipients. Only nine trials provided any information on adverse events. Among these, no adverse events associated with exercise sessions of any ET modality were reported, suggesting safety of the interventions. However, the designs of future trials must incorporate evaluation of safety as an outcome, pre-specifying which parameters will be considered and how data will be collected.

The literature demonstrates that adverse events in exercise-based rehabilitation programs are rare.[61,62] The American Heart Association estimates 1 major cardiovascular complication (myocardial infarction or cardiac arrest) per 81,670 patient-hours of participation in ET programs.[61] Wewege et al.[62] analyzed safety data from 23 studies that compared HIIT

versus MICT or usual care in patients with coronary artery disease and heart failure. They found a single major cardiovascular adverse event occurring in relation to an HIIT session, which equates to 1 major cardiovascular event per 17,083 training sessions (11,333 training hours). One minor cardiovascular adverse event and three noncardiovascular adverse events (primarily musculoskeletal complaints) were also reported for HIIT. Two noncardiovascular events were reported in relation to MICT. Although there is a numerical difference between the ET modalities, events are uncommon with both HIIT and MICT. The low incidence of cardiovascular complications reported by previous studies and observed in this review suggests that, with proper screening and monitoring, the benefits of ET in patients with cardiovascular disease outweigh its risks. However, this must be further explored in HTx recipients, especially considering different ET modalities and timing after the transplant. In this context, even minor and noncardiovascular adverse events must be monitored, as they can influence the treatment and clinical progression of patients.

The certainty in the evidence of network comparisons has been consistently downgraded by the risk of bias within studies. As planned, we performed sensitivity analysis for studies with high risk of bias. We needed to consider six studies, which considerably reduced the number of network comparisons and revealed a need for more methodologically sound and better-performed studies. In the ET scenario, blinding of patients and trainers to the intervention is impossible. However, we suggest that greater care be taken to avoid deviation from protocols, and that reports provide for this aspect. Protocol registration is also strongly recommended, as this makes it possible to assess whether the trial was indeed conducted and its results analyzed according to the pre-specified plan. We also suggest the presentation of more complete reports, with particular attention to aspects of the randomization process, loss to follow-up, and blinding of outcome assessors. For better synthesis of data, it is crucial that future studies report the mean difference from baseline of each group, with the respective standard deviation.

A potential limitation inherent to the design of this study is that indirect comparisons provide observational evidence across randomized trials and may suffer from the potential biases of observational studies, such as confounding bias. The presence of high risk of bias in many studies and imprecision in some effect estimates contributed to the limited confidence in the evidence, which ranged from moderate to very low between comparisons, and limits the clinical applicability of our findings. However, to the best of our knowledge, this systematic review gathers the best available evidence on ET in HTx recipients. Through a network meta-analysis, the effect of different modalities of ET on the VO_2 peak was compared for the first

time. It is important to note that our narrative synthesis of the evidence on adverse events also highlight the need for safety parameters to be prioritized in future RCTs.

In a forthcoming publication, we will present results on other outcomes of clinical relevance in this population. Finally, this study will provide the most robust evidence to date about ET in HTx recipients, and can be used to assist in the development of evidence-based management guidelines for cardiovascular rehabilitation of these special group of patients.

CONCLUSION

Moderate-certainty evidence suggests that CT and HIIT probably increase VO_2 peak at clinically relevant magnitudes and likely are the most efficacious interventions for this purpose, with HIIT probably being superior to MICT in terms of functional capacity improvement in HTx recipients. There is very low certainty evidence that both CT and HIIT may be more efficacious than home-based CT in increasing VO_2 peak. Considering the high risk of bias present in many studies, it is opportune and necessary to conduct future RCTs that consider the methodological aspects pointed out in this document. Finally, although data are limited, no exercise-related adverse events were reported in HTx recipients, which seems to suggest that ET is a safe intervention this scenario.

Patient and public involvement

No patient involvement.

ETHICS AND DISSEMINATION

Given the nature of this study, no ethical approval will be required. The completed systematic review and network meta-analysis will be submitted to a peer-reviewed journal.

Authors Information

Juliana Beust de Lima: orcid.org/0000-0002-5408-2457

Douglas dos Santos Soares: orcid.org/0000-0002-9166-7614

Filipe Ferrari: orcid.org/0000-0001-6929-8392

Nelson Carvas Junior: orcid.org/0000-0003-2168-8927

Gabriel Carvalho: orcid.org/0000-0001-7792-826X

Santiago Alonso Tobar Leitão: orcid.org/0000-0002-4163-7783

Livia Adams Goldriach: orcid.org/0000-0002-1523-4286

Nadine Clausell: orcid.org/0000-0003-4207-3809

Ricardo Stein: orcid.org/0000-0003-2357-5176

Acknowledgements

The authors thank Bárbara Pilatti Piffer, staff librarian at Universidade Federal do Rio Grande do Sul, for her contributions to the design of the search strategies and retrieval of documents. The authors also thank Drs. Andreia Biolo, Daniel Umpierre de Moraes, Luiz Eduardo Ritt, Marcelo Rodrigues dos Santos and Nórton Luís Oliveira for their intellectual contribution to the evaluation and revision of this manuscript.

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TITLES AND LEGENDS

Figures

Figure 1

Title – PRISMA flow diagram: summary of selection process

Legend – Others: full text not available (n=3), conference abstract of included studies (n=13), protocol registers of included studies (n=6) and protocols registers without intervention of interest (n=2).

Figure 2

Title – Network geometry for peak oxygen consumption

Legend – CT: combined training; MICT: moderate intensity continuous training; HIIT: high intensity interval training; RT: resistance training.

Figure 3

Title – Forest plot for mixed comparisons: node-splitting mode for peak oxygen consumption

Legend: Data are presented in difference in means and 95% confidence interval. CT: combined training; MICT: moderate intensity continuous training; HIIT: high intensity interval training; RT: resistance training.

Figure 4

Title – Risk of bias for peak oxygen consumption

Legend – Risk of bias summary: review authors judgements about each risk of bias item for each included study; Risk of bias graph: review authors judgements about each risk of bias item presented as percentages across all included studies.

Figure 5

Title – League table for peak oxygen consumption

Legend – Data are presented in difference in means and 95% confidence interval. Main analysis results in blue; Results of the sensitivity analysis for studies with high risk of bias in green. Positive comparisons in blue favor intervention on the right and negative comparisons in green favor intervention on the right. CT: combined training; MICT: moderate intensity continuous training; HIIT: high intensity interval training; RT: resistance training.

Figure 6

Title – Confidence in the evidence for peak oxygen consumption

Legend – CT: combined training; MICT: moderate intensity continuous training; n: number of studies; HIIT: high intensity interval training; RT: resistance training.

Tables

Table 1

Title – Summary of patients characteristics and eligible outcomes assessed

Legend – ARVD: arrythmogenic right ventricular dysplasia; CON: control; DBP: diastolic blood pressure; DCM: dilated cardiomiopathy; HTx: heart transplantation; HF: heart failure; HR: heart rate; INT: intervention; HRQOL: health-related quality of life; LL: lower limb; NR: not reported; n: number of patients; VO_2 peak: peak oxygen consumption; SBP: systolic blood pressure; SD: standard deviation; UL: upper limb; y: years.

Table 2

Title – Summary of exercise training characteristics

Legend – CT: Combined training; HR: heart rate; HIIT: High-intensity interval training; MICT: Moderate-intensity continuous training; min: minutes; NR: Not reported; RCT: respiratory

compensation point; RM: repetition maximal; RPE: rating of perceived exertion; RT: resistance training; s: seconds; wk: week.

Table 3

Title – Adverse events in studies

Legend – In each line, enumerated publications refer to the same study.

Supplementary material

Supplementary material 1

Title – PRISMA network-metanalysis checklist

Legend ---

Supplementary material 2

Title – Bibliographic databases and search strategies

Legend ---

Supplementary material 3

Title – PRISMA checklist for searching

Legend ---

Supplementary material 4

Title – Records from database

Legend –

Supplementary material 5

Title – Drug therapy

Legend – ACEI, angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker.

Supplementary material 6

Title – Co-interventions information

Legend ---

Supplementary material 7

Title – Studies information

Legend – * Publications with eligible outcome already considered in another manuscript of the same study.

Supplementary material 8

Title – Results of individuals studies

Legend – Pre, post and change values are expressed as mean and standard deviation. * Denotes studies with standard deviation of the change from baseline value estimated.

Supplementary material 9

Title – Contribution of direct evidence for peak oxygen consumption

Legend - CT: combined training; MICT: moderate intensity continuous training; HIIT: high intensity interval training; RT: resistance training.

Supplementary material 10

Title – Pairwise meta-analysis for peak oxygen consumption

Legend ---

CONCLUSÕES E CONSIDERAÇÕES FINAIS

- As evidências sugerem benefícios multifatoriais do TF em pacientes pós-TxC, melhorando a capacidade funcional e repercutindo positivamente em diferentes respostas fisiológicas que podem auxiliar no controle dos fatores de risco cardiovasculares e atenuar os efeitos adversos da terapia imunossupressora.

- Até o presente momento, os ECRs disponíveis investigaram a eficácia de diferentes modalidades de TF sobre o VO_2 pico, qualidade de vida e sobre outras variáveis intermediárias que contribuem para o quadro de intolerância ao exercício e/ou são reconhecidas como marcadores prognósticos em indivíduos com diferentes doenças cardiovasculares.

- Através desta revisão sistemática com meta-análise em rede, moderada certeza na evidência sugere que pacientes pós-TxC que realizam TC ou TIAI apresentam aumento expressivo no VO_2 pico. Considerando nossos achados, provavelmente estas sejam as modalidades de TF que promovem o maior incremento na capacidade funcional destes pacientes. Cabe salientar que em breve apresentaremos resultados sobre o efeito do TF em diversos outros desfechos clinicamente relevantes nesta população.

- Por fim, embora os dados sejam limitados, nenhum evento adverso relacionado ao exercício foi relatado em pacientes pós-TxC. Considerando o alto risco de viés presente na maior parte dos estudos, é oportuna e necessária a condução de ECRs futuros que considerem os aspectos metodológicos apontados neste documento, assim como priorizem avaliações de desfechos de segurança como objetivo primário.

FIGURE 1

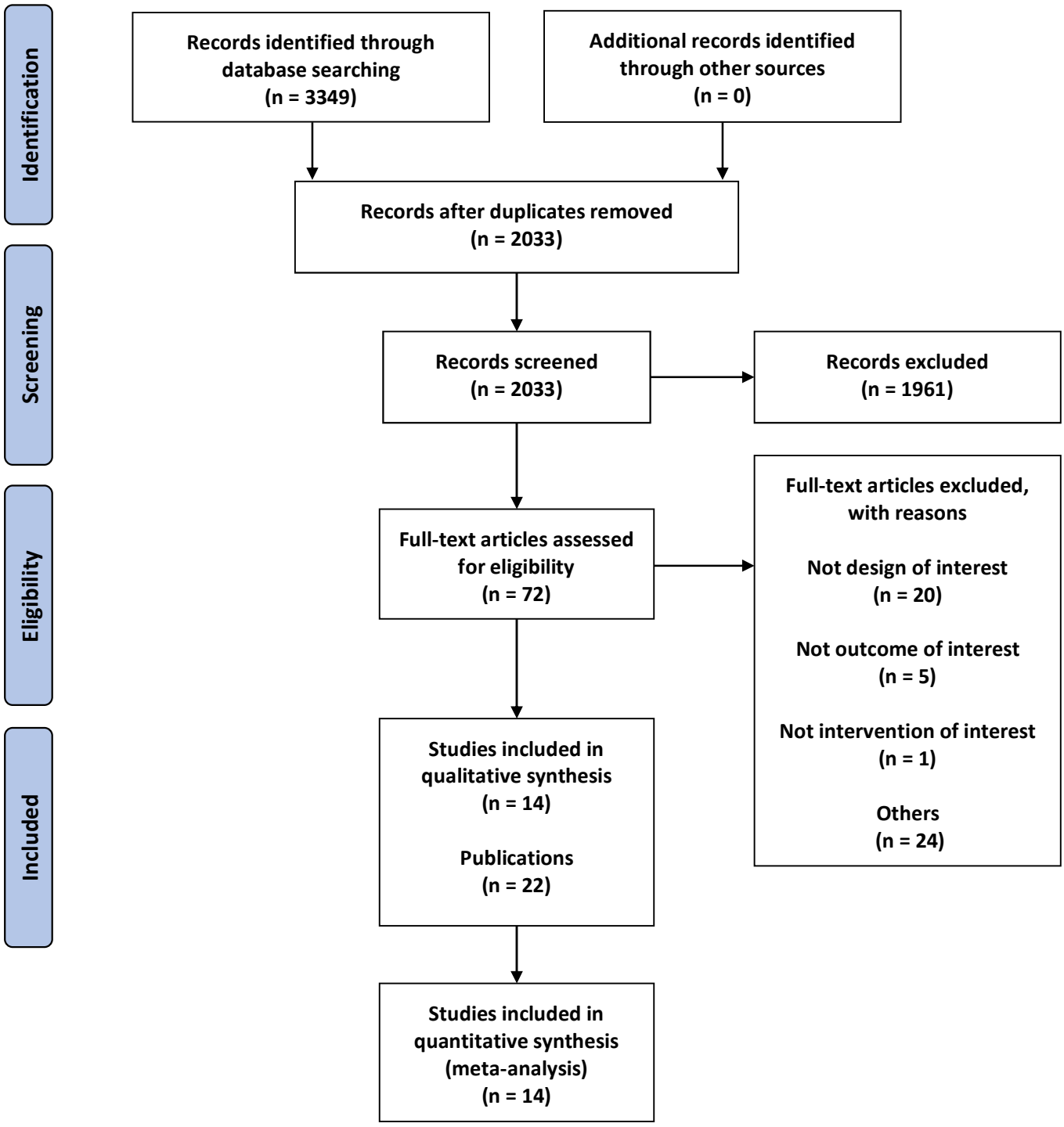
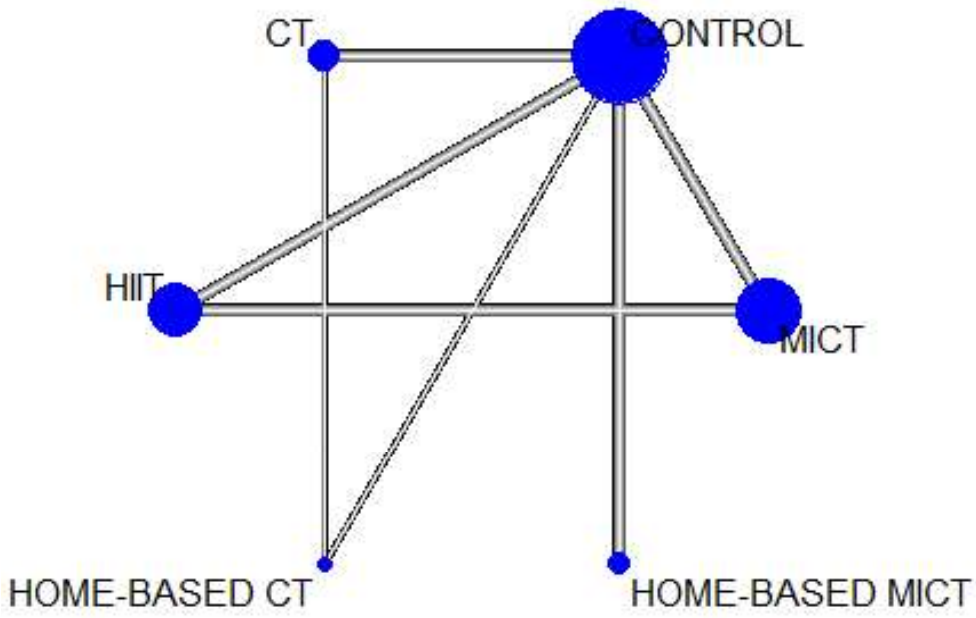

Identification
Screening
Eligibility
Included
Records identified through database searching (n = 3349)
Additional records identified through other sources (n = 0)
Records after duplicates removed (n = 2033)
Records screened (n = 2033)
Records excluded (n = 1961)
Full-text articles assessed for eligibility (n = 72)
Full-text articles excluded, with reasons
Not design of interest (n = 20)
Not outcome of interest (n = 5)
Not intervention of interest (n = 1)
Others (n = 24)
Studies included in qualitative synthesis (n = 14)
Publications (n = 22)
Studies included in quantitative synthesis (meta-analysis) (n = 14)

FIGURE 2

Main analyses



Sensitivity analysis for studies with high risk of bias

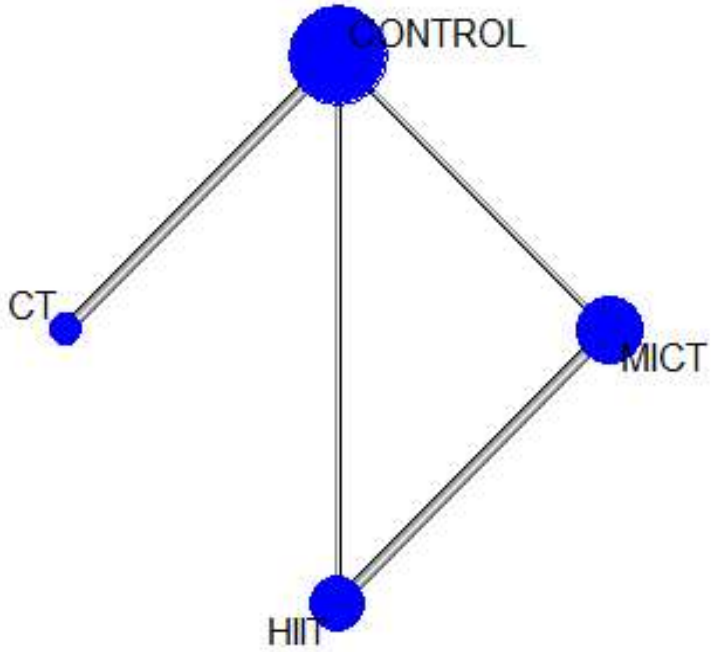


FIGURE 3

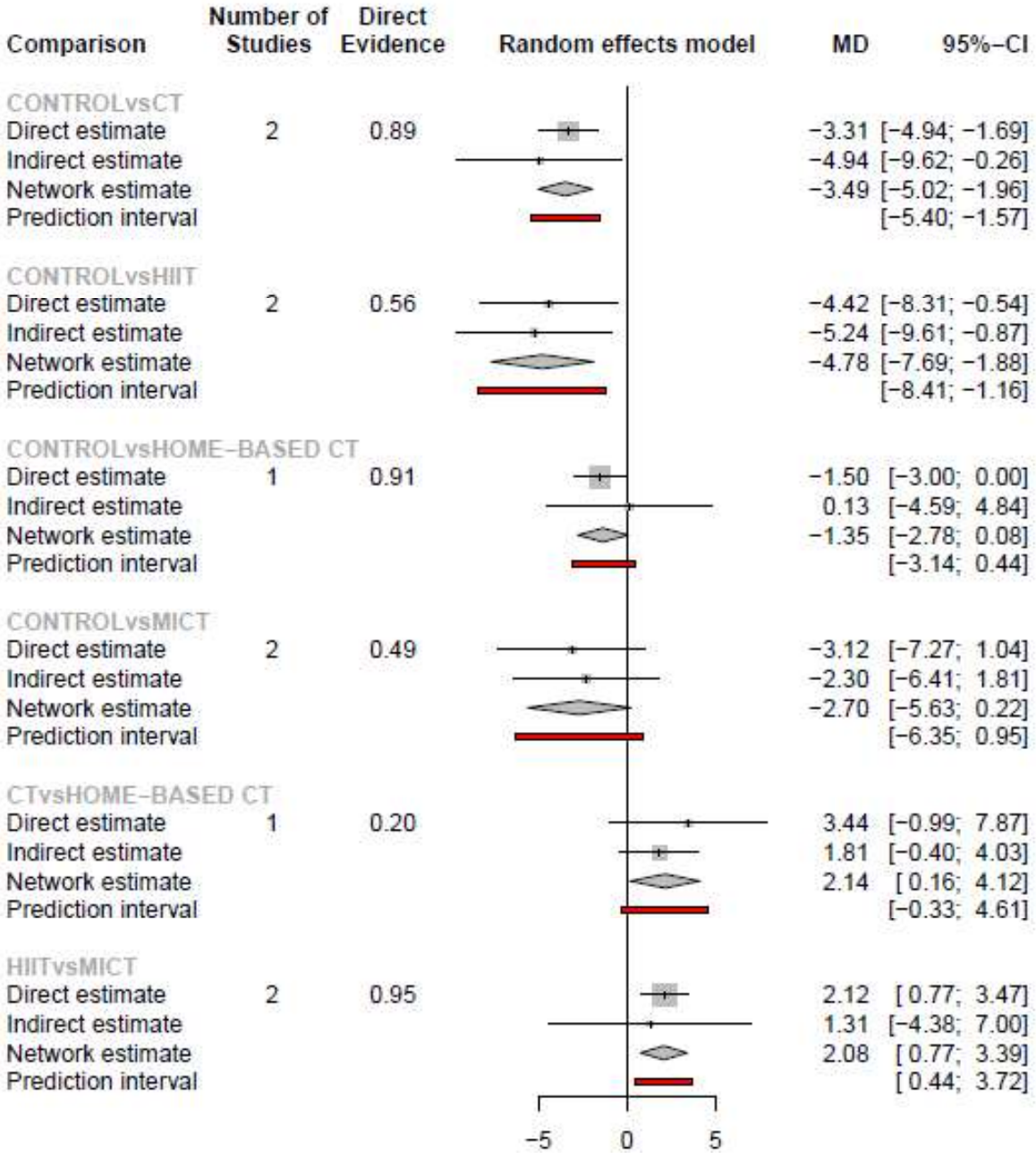
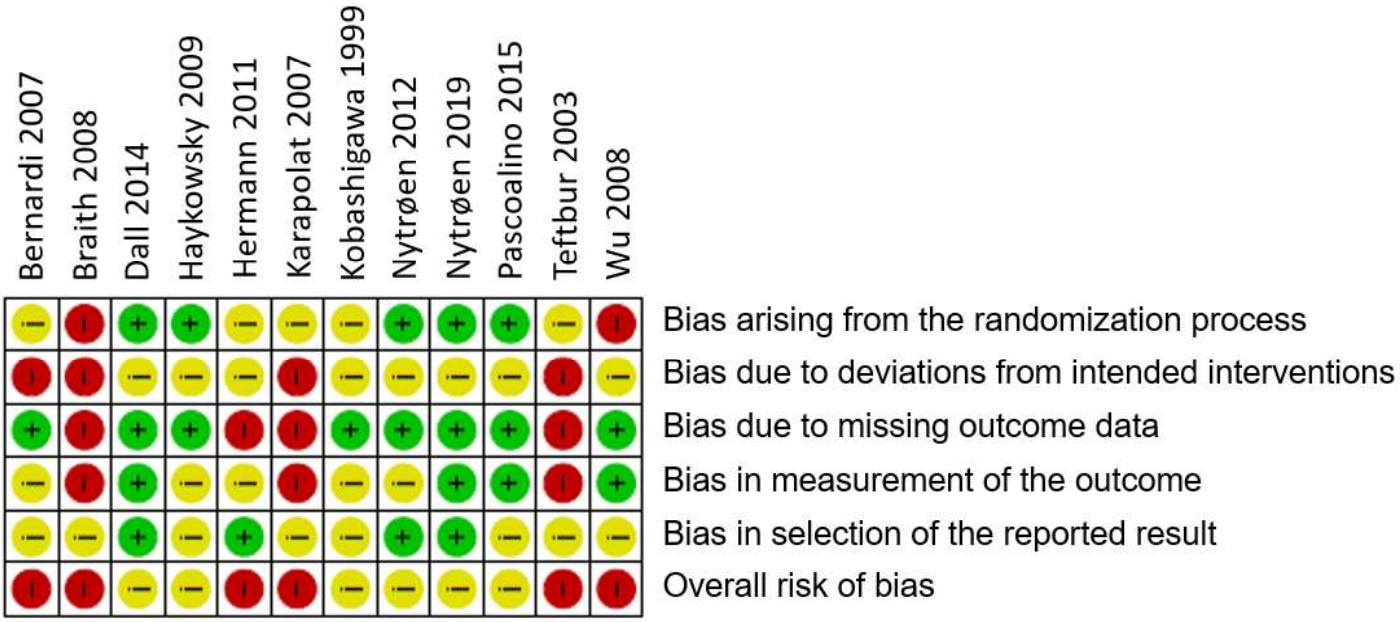

Comparison
Number of Studies
Direct Evidence
Random effects model
MD
95%−CI
CONTROLvsCT
Direct estimate 2 0.89 −3.31 [−4.94; −1.69]
Indirect estimate −4.94 [−9.62; −0.26]
Network estimate −3.49 [−5.02; −1.96]
Prediction interval [−5.40; −1.57]
CONTROLvsHIIT
Direct estimate 2 0.56 −4.42 [−8.31; −0.54]
Indirect estimate −5.24 [−9.61; −0.87]
Network estimate −4.78 [−7.69; −1.88]
Prediction interval [−8.41; −1.16]
CONTROLvsHOME−BASED CT
Direct estimate 1 0.91 −1.50 [−3.00; 0.00]
Indirect estimate 0.13 [−4.59; 4.84]
Network estimate −1.35 [−2.78; 0.08]
Prediction interval [−3.14; 0.44]
CONTROLvsMICT
Direct estimate 2 0.49 −3.12 [−7.27; 1.04]
Indirect estimate −2.30 [−6.41; 1.81]
Network estimate −2.70 [−5.63; 0.22]
Prediction interval [−6.35; 0.95]
CTvsHOME−BASED CT
Direct estimate 1 0.20 3.44 [−0.99; 7.87]
Indirect estimate 1.81 [−0.40; 4.03]
Network estimate 2.14 [0.16; 4.12]
Prediction interval [−0.33; 4.61]
HIITvsMICT
Direct estimate 2 0.95 2.12 [0.77; 3.47]
Indirect estimate 1.31 [−4.38; 7.00]
Network estimate 2.08 [0.77; 3.39]
Prediction interval [0.44; 3.72]
−5
0
5

FIGURE 4


Bernardi 2007
Braith 2008
Dall 2014
Haykowsky 2009
Hermann 2011
Karapolat 2007
Kobashigawa 1999
Nytrøen 2012
Nytrøen 2019
Pascoalino 2015
Teftbur 2003
Wu 2008
Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias

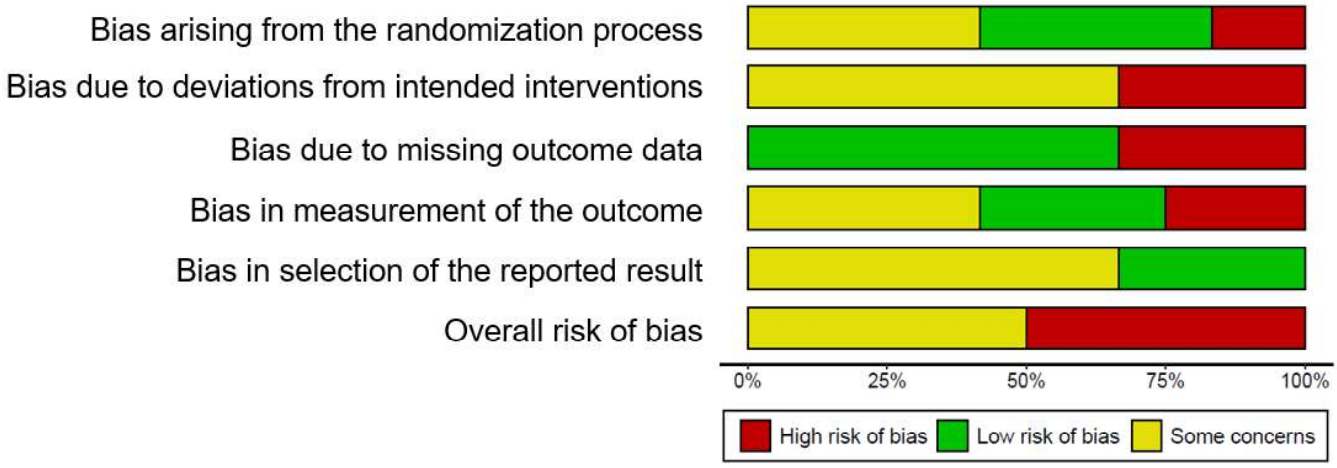

Bias arising from the randomization process
Bias due to deviations from intended interventions
Bias due to missing outcome data
Bias in measurement of the outcome
Bias in selection of the reported result
Overall risk of bias
0%
25%
50%
75%
100%
High risk of bias
Low risk of bias
Some concerns

FIGURE 5

Control	**-3.31 (-4.94 to -1.69)**	**-4.27 (-8.00 to -0.54)**	Lost comparison	Lost comparison	-2.19 (-5.94 to 1.56)
3.49 (1.96 to 5.02)	**CT**	-0.95 (-5.02 to 3.10)	Lost comparison	Lost comparison	1.13 (-2.96 to 5.21)
4.78 (1.88 to 7.69)	1.30 (-1.99 to 4.58)	**HIIT**	Lost comparison	Lost comparison	**2.08 (0.75 to 3.41)**
1.35 (-0.08 to 2.78)	**-2.14 (-4.12 to -0.16)**	**-3.43 (-6.67 to -0.20)**	**Home-Based CT**	Lost comparison	Lost comparison
2.60 (-0.51 to 5.72)	-0.88 (-4.36 to 2.59)	-2.18 (-6.44 to 2.08)	1.25 (-2.17 to 4.68)	**Home-based MICT**	Lost comparison
2.70 (-0.22 to 5.63)	-0.79 (-4.09 to 2.52)	**-2.08 (-3.39 to -0.77)**	1.35 (-1.90 to 4.61)	0.10 (-4.17 to 4.37)	**MICT**

Figure 6

Comparison	n	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating
Mixed evidence								
CONTROL:CT	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
CONTROL:HIIT	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
CONTROL:HOME-BASED CT	1	Major concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Very low
CONTROL:HOME-BASED MICT	2	Major concerns	Undetected	No concerns	Some concerns	Some concerns	No concerns	Very low
CONTROL:MICT	2	Some concerns	Undetected	No concerns	Some concerns	No concerns	No concerns	Low
CT:HOME BASED CT	1	Major concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Very low
HIIT:MICT	2	Some concerns	Undetected	No concerns	No concerns	No concerns	No concerns	Moderate
Indirect evidence								
CT:HIIT	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
CT:HOME-BASED MICT	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
CT:MICT	0	Some concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
HIIT:HOME-BASED CT	0	Major concerns	Undetected	No concerns	No concerns	Some concerns	No concerns	Very low
HIIT:HOME-BASED MICT	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
HOME-BASED CT:HOME-BASED MICT	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
HOME-BASED CT:MICT	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low
HOME-BASED MICT:MICT	0	Major concerns	Undetected	No concerns	Major concerns	No concerns	No concerns	Very low

TABLE 1

Study	Study groups	Sample size (n) Randomized/ analyzed	Men (%)	Age (y) mean ± SD or range	HF etiology (%)	Time post-HTx mean ± SD or range	Outcomes
Bernardi 2007	INT	13 / 13	NR	50 ± 3	NR	6 months	VO_2 peak, HR rest
	CON	11 / 11	NR	53 ± 4	NR		
Braith 1998	INT	7 / 7	NR	54 ± 3	NR	2 months	Fat mass, lean mass, muscle strength (UL and LL)
	CON	7 / 7	NR	51 ± 8	NR		
Braith 2005	INT	8/7	100%	52 ± 2	Ischemic (57%) DCM (43%)	2 months	Muscle strength (UL and LL)
	CON	7/6	100%	53 ± 2	Ischemic (67%) DCM (33%)		
Braith 2008	INT	10 / 9	78%	54.4 ± 13.1	Ischemic (56%)	67.3 ±11.2 days	VO_2 peak, endothelial function
	CON	10 / 7	86%	54.3 ± 9.5	Ischemic (57%)	73.6 ± 30.6 days	
Christensen 2012	INT	14 / 14	NR	53.4 ± 11.4	Valvular (7%) Non-ischemic (57%) Ischemic (36%)	6.8 ± 4.0 years	HRQOL
	CON	13 / 13	NR	47.3 ± 17.9	Non-ischemic (77%) Ischemic (23%)	7.0 ± 5.5 years	
Dall 2014	INT-CON	8	75%	51.9 (33–70)	NR	6.4 (1-17) years	VO_2 peak, HR (rest, peak, reserve and recovery)
	CON-INT	9			NR		
Dall 2015	INT-CON	8	75%	51.9 (33–70)	NR	6.4 (1-17) years	Endothelial function, HRQOL
	CON-INT	9			NR		

Haykowsky 2009	INT	22 / 22	77%	57 ± 10	Ischemic (45%) Non-ischemic (55%)	5.4 ± 4.9 years	VO_2 peak, HR peak, SBP peak, DBP peak, endothelial function, muscle strength (UL and LL), lean mass
	CON	21 / 19	86%	59 ± 11	Ischemic (76%) Non-ischemic (23%)	4.4 ± 3.3 years	
Hermann 2011	INT	14 / 14	86%	53 ± 11	Ischemic (36%) DCM (57%) Valvular (7%)	6.8 ± 4.0 years	VO_2 peak, endothelial function
	CON	13 / 13	77%	47 ± 18	Ischemic (23%) DCM (77%)	7.0 ± 5.5 years	
Karapolat 2007	INT	38 13	93%	35.6 ± 12.9	NR	16.7 ± 17.6 months	VO_2 peak, HRQOL
	CON	15	85%	45.2 ± 13.1	NR	14.5 ± 17.2 months	
Karapolat 2008	INT	20 / 13	92.3%	35.6 ± 12.9	Ischemic (18%)	16.7 ± 17.6 months	HR (reserve and recovery)
	CON	20 / 15	93.3%	45.2 ± 13.1	Ischemic (29%)	14.5 ± 17.2 months	
Kobashigawa 1999	INT	14 / 14	79%	55 ± 8	Ischemic (29%)	2 weeks	VO_2 peak, VE/VO_2 slope, VE/VCO_2 slope, HR (rest and peak), SBP peak, muscle strength (LL)
	CON	13 / 13	62%	50 ± 12	Ischemic (54%)		
Monk-Hansen 2014	INT	15 / 13	85%	52 ± 11	NR	7.4 (1.6 – 18.1) years	HR (rest and peak)
	CON	15 / 10	70%	47 ± 19	NR		
Nytröen 2012	INT	26 / 24	67%	48 ± 17	NR	4.3 ± 2.4 years	VO_2 peak, HR peak, rest, reserve and recovery), BORG peak, SBP peak, DBP peak, VO2/HR, VE/VCO2 slope, muscle strength (LL), fat mass, HRQOL
	CON	26 / 24	71%	53 ± 14	NR	3.8 ± 2.1 years	

Nytröen 2019	INT	39 / 37	76%	50 ± 12	Cardiomiopathy (57%) Ischemic (38%) Other (5%)	11 (7-16) weeks	VO_2 peak, muscle strength (LL), endothelial function, BORG peak, VO2/HR, VE/VCO2 slope, HR (peak, reserve and recovery), fat mass, lean mass
	CON	42 / 41	71%	48 ± 14	Cardiomiopathy (75%) Ischemic (15%) Other (10%)		
Pascoalino 2015	INT	33 / 31	74%	45 ± 3	NR	6.3 ± 1.3 years	HR (rest, peak and recovery), SBP peak, DBP peak, VO_2 peak, VE/VCO2 slope
	CON	9 / 9	55%	45 ± 6	NR	5.8 ± 1.6 years	
Pierce 2008	INT	10 / 8	75%	53.5 ± 13.6	Ischemic (63%)	68.3 ± 10.4 days	HR (rest and peak), BORG peak
	CON	10 / 6	83%	54.2 ± 6.4	Ischemic (50%)	78.3 ± 21.1 days	
Rolid 2020	INT	39 / 37	76%	50 ± 12	Cardiomiopathy (57%) Ischemic (38%) Other (5%)	11 ± 2 weeks	HRQOL
	CON	42 / 41	71%	48 ± 14	Cardiomiopathy (75%) Ischemic (15%) Other (10%)		
Tegtbur 2003	INT	16 / 20	95%	55 ± 7	Ischemic (30%) DCM (65%) ARVD (5%)	5.1 ± 2.2 years	VO_2 peak, fat mass, HR (rest and peak), SBP peak, DBP peak, BORG peak, HRQOL
	CON	15 / 12	92%	54 ± 8	Ischemic (33%) DCM (58%) ARVD (8%)	4.5 ± 2.3 years	

Wu 2008	INT	18 / 14	79%	60.6 ± 6.2	DCM (50%) Ischemic (36%) Rheumatic (14%)	18.6 ± 21 months	Muscle strength (LL), HR (rest and peak), VO_2 peak, BORG peak, HRQOL
	CON	19 / 23	78%	51.6 ± 12.8	DCM (48%) Ischemic (48%) Marfan syndorme (4%)	31.4 ± 23 months	

TABLE 2

Study	Exercise modalities	Intensity	Intervention	Frequency (times a wk)	Time (min)	Length (wk)	Equipment	Supervision	Control Group
Bernardi 2007	Home-based MICT	60-70% of VO_2 peak	30 min MICT	5	30	24	Cycle ergometer	No	No exercise
Braith 1998	RT	50% of 1-RM	5 min warm-up; 1 set 10-15 reps (resistance exercises); 5 min cool-down	3	NR	24	Resistance machines and treadmill	Yes	No exercise
Braith 2005	RT	50% 1-RM	5 min warm-up; 1 set 10-15 reps (8 resistance exercises)	2	NR	24	Resistance machines and treadmill	Yes	No exercise
Braith 2008	MICT	11-13 of BORG RPE scale progressed to 12-14	5 min warm-up; 30-40 min MICT; 5 min cool-down	3	40-50	12	Treadmill	Yes	Encouragement to regular walking
Christensen 2012	HIIT	80%, 85% and 90% of VO_2 peak	10 min warm-up; 42 min HIIT (blocks of 4 min, 2 min and 30 s; recovery 1-2 min); 10 min staircase running up; Recovery walking down	3	≈ 62	8	Cycle ergometer and staircase running	Yes	No exercise
Dall 2014	HIIT	>80% of VO_2 peak and approximately 60% of VO_2 peak	10 min warm-up; 16 min (intervals of 4 min, 2 min and 1 min) separated by a 2 min active rest (sessions lasted 32 min); 10 min cool-down	3	≈ 52	12	Cycle ergometer	Yes	MICT
	MICT	60-70% of VO_2 peak	45 min MICT; 10 min cool-down		45				

Dall 2015	HIIT	>80% of VO_2 peak and approximately 60% of VO_2 peak	10 min warm-up; 16 min (intervals of 4 min, 2 min and 1 min) separated by a 2 min active rest (sessions lasted 32 min); 10 min cool-down	3	≈ 50	12	Cycle ergometer	Yes	MICT
	MICT	60-70% of VO_2 peak	45 min MICT; 10 min cool-down		45				
Haykowsky 2009	CT	60-80% of VO_2 peak (MICT); 90-100% of peak power (HIIT)	1-8 wk: 30-45 min MICT, 5 times a wk; 9-12 wk: 45 min MICT, 3 times a wk and HIIT, 10-25 reps of 30 s followed by 60 s rest, 2 times a wk	5	30-45	12	Treadmill and cycle ergometer	Yes	No exercise
		50% of maximal strength (RT)	1-2 sets 10-15 reps	2	NR		NR		
Hermann 2011	HIIT	80%, 85% and 90% of VO_2 peak	10 min warm-up; 42 min HIIT (blocks of 4 min, 2 min and 30 s; recovery 1-2 min); 10 min staircase running up; Recovery walking down	3	≈ 62	8	Cycle ergometer and staircase running	Yes	No exercise

Karapolat 2007	Home-based CT	60%-70% of VO_2 peak (MICT)	1-8 weeks: 30 min MICT; Breathing, flexibility and relaxation exercises; Walking program	3	≈ 90	8	Treadmill and cycle ergometer	No	Home-based CT
		Progressively heavier "light weights" (RT)	3-8 weeks: resistance exercises						
	Hospital-based CT	60%-70% of VO_2 peak (MICT)	1-8 weeks: 30 min MICT; Breathing, flexibility and relaxation exercises; Walking program				Treadmill and cycle ergometer	Yes	
		Progressively heavier "light weights" (RT)	3-8 weeks: resistance exercises						
Karapolat 2008	Home-based CT	60% to 70% of VO_2 peak (MICT)	1-8 weeks: 30 min MICT; Breathing, flexibility and relaxation exercises; Walking program	3	≈ 90	8	Treadmill and cycle ergometer	No	Home-based CT
		Progressively heavier "light weights" (RT)	3-8 weeks: resistance exercises						
	Hospital-based CT	60% to 70% of VO_2 peak (MICT)	1-8 weeks: 30 min MICT; Breathing, flexibility and relaxation exercises; Walking program				Treadmill and cycle ergometer	Yes	
		Progressively heavier "light weights" (RT)	3-8 weeks: resistance exercises						

Kobashigawa 1999	CT	MICT RT: NR	≥ 30 min MICT Resistance exercises	3	≥ 30 min NR	24	Treadmill, cycle and arm ergometer	Yes	Written guidelines for exercise
Monk-Hansen 2014	HIIT	80%, 85% and 90% of VO_2 peak	10 min warm-up; 42 min HIIT (blocks of 4 min, 2 min and 30 s; recovery 3 min, 1 min and 30 s); 10 min staircase running up; Recovery walking-down	3	≈ 62	8	Cycle ergometer and staircase running	Yes	No exercise
Nytröen 2012	HIIT	85-95% HR peak and active recovery 11-13 RPE BORG	10 min warm-up; 4 x intensity interval blocks (4 min) and 4 x blocks of active recovery (3 min)	3	≈ 38 min	24 supervised/ 48 total	Treadmill ergometer	Yes (partly)	No exercise
Nytröen 2019	HIIT	85-95% HR peak (16-18 BORG) and active recovery 60-70 HR peak (11-13 BORG)	1-3 months: 1 HIIT session, 1 RT session, 1 CT session; 4-6 months: 2 HIIT sessions, 1 RT session; 7-9 months: 3 HIIT sessions; HIIT: 10 min warm-up; 4 blocks 2-4 min and 3 blocks 3 min of active recovery; 5 min cool-down	2-3	≈40 min	36	NR	Yes	MICT
	MICT	≤ 80% peak effort (12-15 BORG)	10 min warm-up; 25 min MICT; 5 min cool-down; RT for large muscle groups						

Pascoalino 2015	MICT	80% of the RCP HR	5 min of warm-up; 40 min MICT; 5 min cool-down	3	60	12	Treadmill	2 yes; 1 no	No exercise
Pierce 2008	MICT	11 – 13 BORG RPE; 12 – 14 BORG RPE	1-4 weeks: 30 min MICT; 5-12 weeks: 35-40 min MICT	3	30-40	12	Treadmill	Yes	Encouragement to regular walking
Rolid 2020	HIIT	85-95% HR peak and active recovery 60-70 HR peak	1-3 months: 1 HIIT session, 1 RT session, 1 CT session; 4-6 months: 2 HIIT sessions, 1 RT session; 7-9 months: 3 HIIT sessions; HIIT: 10 min warm-up; 4 blocks 2-4 min and 3 blocks 3 min of active recovery; 5 min cool-down	2-3	≈40 min	36	NR	Yes	MICT
	MICT	≤ 80% peak effort	10 min warm-up; 25 min MICT; 5 min cool-down; RT for large muscle groups						
Tegtbur 2003	Home-based MICT	10% below the anaerobic threshold	6 min warm-up; 28 exercise; 2 min cool-down	Every 2 days	≈ 28	48	Cycle ergometer	No	No exercise
Wu 2008	Home-based CT	60-70% VO_2 peak (MICT)	5 min warm-up; 15–20 min MICT (walking); 10 min of stepping exercise with a stool; 5 min cool-down	Least 3	35-40	8	NR	No	No exercise
		Light (RT)	8 resistance exercises		NR				

TABLE 3

Study	Reporting of adverse events
Braith 2008	"No adverse events occurred during exercise testing (...)"
(1) Dall 2014 *(2) Dall 2015*	(1) "No adverse events were associated with either the HIIT or the CON intervention." (2) "No severe adverse events were associated with participating in either of the 2 interventions."
Hermann 2011	"No serious adverse events were observed during the study."
Haykowsky 2009	"No adverse events were associated with the SET program."
Kobashigawa 1999	"Patients tolerated exercise training with no adverse clinical events."
(1*) Nytröen 2012* *(*2) *Nytröen 2013* (3) *Rustad 2014*	(1) "One patient in the CG suffered from an MI resulting in HF and was lost to follow-up. There were no other serious adverse events in any of the groups during the time of follow-up and there were no incidences of musculoskeletal injuries in the EG." (2) "Safety parameters regarding the population in this study have been described elsewhere." (3) "There were no adverse events during testing, or during the intervention period in either group."
(1) *Nytröen 2019* (2) *Rolid 2020*	(1) "No serious exercise related adverse event occurred in either group during the intervention period." (2) "There were no differences between groups regarding rejections or serious/adverse events during the intervention period."
Tegtbur 2003	"Bei hoher Compliance und ohne kardiovaskuläre Zwischenfälle ergaben sich folgende Hauptresultate (...)"
Wu 2008	"None had cardiovascular events during the 8 weeks of study." "No major adverse events or mortality developed in the study period."

SUPPLEMENTARY MATERIAL 1

PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	***53***
ABSTRACT			***57***
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.*	***59***
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	***60***
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	***61***
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the*	***61***

		treatment network, and note whether any have been clustered or merged into the same node (with justification).	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	***64***
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	***64***
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	***65***
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	***65***
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	***65***
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	***66***
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	***66***
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*	***67***
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*	***67***
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	***67***
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	***68***

Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	***68***
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	***68***
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	***70***
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	***70***
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	***69***
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	***70***
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	***71***
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	***71 and 74***
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests,	***72***

		or summary of inconsistency estimates from different parts of the treatment network.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	***72***
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth).	***73***
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	***74***
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	***74***
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	***79***
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	***54***

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.

SUPPLEMENTARY MATERIAL 2

PubMed/MEDLINE
(((heart transplantation[MeSH] OR heart transplant*[tw] OR cardiac transplant*[tw] OR heart recipient*[tw] OR heart transplant*[tw] OR new heart[tw] OR heart grafting[tw] OR cardiac grafting[tw] OR cardiac allograft*[tw] OR cardiac graft*[tw] OR heart graft*[tw])) AND ((exercise[MeSH] OR exercise*[tw] OR physical training[tw] OR physical exercise*[tw] OR high-intensity interval training*[tw] OR high intensity interval training*[tw] OR high-intensity intermittent exercise*[tw] OR high-intensity exercise*[tw] OR sprint interval training*[tw] OR resistance training[MeSH] OR strength training[tw] OR aerobic exercise*[tw] OR aerobic training*[tw] OR physical endurance[MeSH] OR resistance exercise*[tw] OR exercise therapy[MeSH] OR exercise therap*[tw] OR combined training[tw] OR concurrent training[tw] OR concurrent exercise*[tw] OR circuit-based exercise[MeSH] OR circuit based exercise*[tw] OR circuit training[tw] OR combined training[tw] OR combined exercise*[tw] OR exercise-based rehabilitation[tw] OR training based rehabilitation[tw] OR isometric exercise*[tw] OR home-based exercise*[tw] OR home-based training[tw] OR rehabilitation exercise*[tw] OR weight training[tw] OR weight exercise*[tw] OR weight lifting*[tw] OR weightlifting exercise[tw] OR weightlifting exercises[tw]))) AND (("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "clinical trial"[pt] OR "random allocation"[mh] OR "double-blind method"[mh] OR "clinical trial"[pt] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]))
Cochrane
#1 MeSH descriptor: [Heart Transplantation] explode all trees
#2 "heart transplantation*" OR "cardiac transplant*" OR "heart recipient*" OR "heart transplant*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*"
#3 #1 or #2
#4 MeSH descriptor: [Exercise] explode all trees
#5 MeSH descriptor: [Exercise Therapy] explode all trees
#6 MeSH descriptor: [Physical Fitness] explode all trees
#7 MeSH descriptor: [High-Intensity Interval Training] explode all trees
#8 MeSH descriptor: [Resistance Training] explode all trees
#9 MeSH descriptor: [Physical Endurance] explode all trees
#10 MeSH descriptor: [Circuit-Based Exercise] explode all trees

#11 exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*"

#12 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 #3 and #12 in Trials

Scopus

#1 TITLE-ABS-KEY("heart transplantation*" OR "cardiac transplant*" OR "heart recipient*" OR "heart transplant*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*")

#2 TITLE-ABS-KEY(exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*")

#3 (INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo")) OR (TITLE-ABS-KEY (("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE-ABS (clinical trial* OR trial* OR rct* OR random* OR blind*))

SPORTDiscus

(DE "HEART transplantation" OR "heart transplant*" OR "cardiac transplant*" OR "heart recipient*" OR "cardiac allograft") AND (DE "EXERCISE" OR DE "RESISTANCE training" OR DE "PHYSICAL fitness" OR DE "EXERCISE therapy"

OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*")

CINAHL

(MH "heart transplantation" OR "heart transplantation*" OR "cardiac transplant*" OR "heart recipient*" OR "heart transplant*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*") AND (MH "Exercise" OR MH "Resistance Training" OR MH "Therapeutic Exercise" OR OR exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*")

Web of Science

ALL=("heart transplant*" OR "cardiac transplant*" OR "heart recipient*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*") AND ALL=(exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*") AND (TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*))

Embase

('heart transplantation'/exp OR 'cardiac transplantation' OR 'heart allograft' OR 'heart allotransplantation' OR 'heart heterograft' OR 'heart heterotransplantation' OR 'heart

homograft' OR 'heart homotransplantation' OR 'heart orthotopic transplantation' OR 'heart tissue transplantation' OR 'heart transplantation' OR 'heart ventricle transplantation' OR 'human heart transplantation' OR 'transplantation, heart' OR 'heart graft'/exp OR 'cardiac graft' OR 'cardiac transplant' OR 'heart graft' OR 'heart graft survival' OR 'heart transplant' OR 'transplant, heart') AND ('aerobic exercise'/exp OR 'aerobic dance' OR 'aerobic dancing' OR 'aerobic exercise' OR 'aerobics' OR 'aerobics exercise' OR 'dancing, aerobic' OR 'exercise, aerobic' OR 'low impact aerobic exercise' OR 'low impact aerobics' OR 'step aerobics' OR 'exercise'/exp OR 'biometric exercise' OR 'effort' OR 'exercise' OR 'exercise capacity' OR 'exercise performance' OR 'exercise training' OR 'exertion' OR 'fitness training' OR 'physical conditioning, human' OR 'physical effort' OR 'physical exercise' OR 'physical exertion' OR 'restraint, physical' OR 'resistance training'/exp OR 'resistance exercise' OR 'resistance exercise training' OR 'resistance training' OR 'strength training' OR 'weight bearing exercise' OR 'kinesiotherapy'/exp OR 'sktm (specialized kinesitherapeutic methodology)' OR 'corrective exercise' OR 'exercise movement techniques' OR 'exercise therapy' OR 'exercise treatment' OR 'kinesiotherapeutic intervention' OR 'kinesiotherapeutic method' OR 'kinesiotherapeutic procedure' OR 'kinesiotherapeutic technique' OR 'kinesiotherapeutical treatment' OR 'kinesiotherapy' OR 'kinesitherapeutic exercises' OR 'kinesitherapeutic intervention' OR 'kinesitherapeutic method' OR 'kinesitherapeutic methodology' OR 'kinesitherapeutic procedure' OR 'kinesitherapeutic technique' OR 'kinesitherapeutic treatment' OR 'kinesitherapeutical treatment' OR 'kinesitherapy' OR 'specialised kinesitherapeutic methodology' OR 'specialized kinesitherapeutic methodology' OR 'therapeutic exercise' OR 'therapy, exercise' OR 'treatment, exercise') AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*)

Pedro

"Heart transplant"

ClinicalTrials.gov

Condition or disease: heart transplant

Study type: interventional studies (clinical trials)

Study results: all studies

Status: active, not recruiting, terminated, completed, unknown status

Age group: adult and older adult

Sex: all

Intervention/treatment: exercise

REBEC

Trials containing the terms: “heart transplant” and exercise Study type: Interventional Inclusion gender: both Recruitment situation: recruitment completed, premature termination and complete data analysis Minimum age for inclusion: 18 years
OpenGrey – grey literature
“heart transplant” and exercise
Google Scholar – grey literature
“heart transplant” and exercise We will review the first 300 search results.

SUPPLEMENTARY MATERIAL 3

Section/topic	#	Checklist item	Location(s) Reported
INFORMATION SOURCES AND METHODS			
Database name	1	Name each individual database searched, stating the platform for each.	64
Multi-database searching	2	If databases were searched simultaneously on a single platform, state the name of the platform, listing all of the databases searched.	-
Study registries	3	List any study registries searched.	Supplementary material 7
Online resources and browsing	4	Describe any online or print source purposefully searched or browsed (e.g., tables of contents, print conference proceedings, web sites), and how this was done.	64
Citation searching	5	Indicate whether cited references or citing references were examined, and describe any methods used for locating cited/citing references (e.g., browsing reference lists, using a citation index, setting up email alerts for references citing included studies).	64
Contacts	6	Indicate whether additional studies or data were sought by contacting authors, experts, manufacturers, or others.	64
Other methods	7	Describe any additional information sources or search methods used.	64
SEARCH STRATEGIES			
Full search strategies	8	Include the search strategies for each database and information source, copied and pasted exactly as run.	Supplementary material 2
Limits and restrictions	9	Specify that no limits were used, or describe any limits or restrictions applied to a search (e.g., date or time period, language, study design) and provide justification for their use.	64
Search filters	10	Indicate whether published search filters were used (as originally designed or modified), and if so, cite the filter(s) used.	-

Prior work	11	Indicate when search strategies from other literature reviews were adapted or reused for a substantive part or all of the search, citing the previous review(s).	-
Updates	12	Report the methods used to update the search(es) (e.g., rerunning searches, email alerts).	-
Dates of searches	13	For each search strategy, provide the date when the last search occurred.	64
PEER REVIEW			
Peer review	14	Describe any search peer review process.	65
MANAGING RECORDS			
Total Records	15	Document the total number of records identified from each database and other information sources.	Supplementary material 4
Deduplication	16	Describe the processes and any software used to deduplicate records from multiple database searches and other information sources.	65

PRISMA-S: An Extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews
Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, Koffel JB, PRISMA-S Group.
Last updated February 27, 2020.

SUPPLEMENTARY MATERIAL 4

Database	Number of records
Main search	
PubMed/MEDLINE	781
Cochrane	211
Scopus	756
SPORTDiscus	115
CINAHL	148
Web of Science	632
Embase	655
Pedro	50
Gray literature and registers	
ClinicalTrials.gov	7 (1 additional)
REBEC	0
OpenGrey	0
Google Schoolar	0

SUPPLEMENTARY MATERIAL 5

Study	Medications
Bernardi 2007	Control group: Cyclosporin, 10/11; Azathioprine, 10/11; Oral steroids, 10/11; Diuretics, 5/11; ACEI, 3/11; Calcium-antagonists, 4/11; Beta-blockers, 0/11. Exercise training group: Cyclosporin, 13/13; Azathioprine, 13/13; Oral steroids, 13/13; Diuretics, 6/13; ACEI, 5/13; Calcium-antagonists, 5/13; Beta-blockers, 1/13. *number of patients.
Braith 1998	"The heart transplant recipients had biatrial anastomosis at the time of transplantation and were receiving standard triple-drug immunosuppressive therapy with cyclosporine, prednisone, and azathioprine." "Glucorticoid therapy. Heart transplant recipients at our institution receive 1,000 mg of methylprednisolone (Upjohn, Kalamazoo, MI) intravenously during the transplantation surgery and 375 mg/24 h methylprednisolone intravenously the first postoperative day. Methylprednisolone is reduced to 250 mg/24 h the second postoperative day and 125 mg/24 h the third postoperative day. Oral prednisone (1 mg·kg-1·d-1) is initiated on the fourth postoperative day. During the first 6 wk after surgery the daily prednisone dose is tapered by 10 mg each week in transplant recipients who remain rejection free. The daily prednisone dose is further reduced by 5 mg after the 6-wk biopsy and by another 5 mg after the 8-wk biopsy. Thereafter, in the absence of rejection, the daily prednisone dose is decreased by 2.5 mg every 2 wk to a target dose of 10 mg·d-1 at 20 wk post-transplantation. Further prednisone reduction is not attempted until 1 yr after transplantation. Episodes of acute graft rejection, as determined by routine surveillance endomyocardial biopsy, are treated with enhanced immunosuppression including increased doses of iv methylprednisolone or oral prednisone."
Braith 2005	"All heart transplant recipients had biatrial anastomosis at the time of transplantation and were receiving triple-drug immunosuppression therapy with cyclosporine, prednisone, and azathioprine. Cyclosporine dose was titrated to maintain whole blood trough levels of approximately 300 ng/ml."

	"Glucocorticoid therapy: Heart transplant recipients all received 1,000 mg of methylprednisolone (Solumedrol, Pharmacia & UpJohn, New York, New York) intravenously during the transplantation surgery and 375 mg/24 hours of methylprednisolone intravenously on the first postoperative day. Methylprednisolone was reduced to 250 mg/24 hours on the second postoperative day and to 125 mg/24 hours on the third postoperative day. Oral prednisone (1 mg/kg body weight/day) was initiated on the fourth postoperative day. During the first 6 weeks after transplantation, the daily prednisone dose was tapered by 20 mg each week in transplant recipients who remained rejection free. The daily prednisone dose was further reduced by 10 mg after week 6, and by 5 mg after week 8. Thereafter, in the absence of rejection, the daily prednisone dose was decreased by 2.5 mg every 2 weeks until prednisone was discontinued or rejection occurred. Episodes of acute rejection, as determined by routine surveillance endomyocardial biopsy, were treated with enhanced immunosuppression, including increased doses of intravenous methylprednisolone or oral prednisone."
Braith 2008	Study presents institutional protocol for immunosuppressive therapy. Control group: Cyclosporine therapy, 6 (86%); Cyclosporine dose, mg/day 379.2 ± 123.0; Tacrolimus therapy, 1 (14%); Prednisone therapy, 7 (100%); Prednisone dose, mg/day 24.3± 16.7; Mycophenolate mofetil therapy, 7 (100%); Mycophenolate mofetil dose, mg/day 2714.3 ± 393; Statin therapy, 7 (100%); ACEI/ARB therapy, 3 (43%). Exercise training group: Cyclosporine therapy, 7 (78%); Cyclosporine dose, mg/day 328.6 ± 77.0; Tacrolimus therapy, 2 (22%); Prednisone therapy, 9 (100%); Prednisone dose, mg/day 22.8 ± 6.1; Mycophenolate mofetil therapy, 9 (100%); Mycophenolate mofetil dose, mg/day 2800.0 ± 632; Statin therapy, 9 (100%); ACEI/ARB therapy, 5 (56%). * number of patients and percentage; mean and standard deviation.
Christensen 2012	Not reported in this publication
Dall 2014	"Of the patients, nine were on nondihydropyridine calcium channel antagonists, nine on angiotensin converting enzyme inhibitors/ angiotensin receptor antagonists and one patient was on beta blockers."

	Total: Cyclosporine/tacrolimus 81/6%; Mycophenolate mofetil/everolimus 81/50%; Prednisolone 44%; Antihypertensive medication 94%."
Dall 2015	"Of the patients, nine were on nondihydropyridine calcium channel antagonists, nine on angiotensin converting enzyme inhibitors/ angiotensin receptor antagonists and one patient was on beta blockers." Total: Cyclosporine/tacrolimus 81/6%; Mycophenolate mofetil/everolimus 81/50%; Prednisolone 44%; Antihypertensive medication 94%."
Hermann 2011	Exercise training group: Corticosteroid dose (mg/day) 2.7 ± 2.5; Ciclosporine dose (mg/day) 171 ± 65; Tacrolimus dose (mg/day) 7.0 ± 2.8; Loop-diuretics, 8 (57%); Antihypertensive treatment, 12 (86%); ACEI, 1 (7%); ARB 9 (64%); Beta-blockers, 2 (14%); Dihydropyridines 3 (21%); Insulin, 2 (14%); Sulfonylurea, 0; Metformin, 1 (7%); Statins, 12 (86%). Control group: Corticosteroid dose (mg/day) 4.2 ± 2.4; Ciclosporine dose (mg/day) 161 ± 69; Tacrolimus dose (mg/day) 7.8 ± 2.6; Loop-diuretics 4 (31%); Antihypertensive treatment, 12 (92%); ACEI, 3 (23%); ARB, 5 (38%); Beta-blockers, 4 (31%); Dihydropyridines, 8 (62%); Insulin, 0; Sulfonylurea, 1(8%); Metformin, 0; Statins, 12 (92%). * number of patients and percentage; mean and standard deviation.
Haykowsky 2009	Control goup: Azathioprine, 1 (5%); Mycophenolate mofetil, 15 (71%); Cyclosporine, 15 (71%); Tacrolimus, 6 (29%); Sirolimus, 3 (14%); Everolimus, 1 (5%); Prednisone, 6 (29%); Agiotensin converting enzyme inhibitor, 16 (76%); Angiotensin II receptor antagonist, 2 (10%); Alpha blocker, 1 (5%); Alpha II agonist, 1 (5%); Beta blocker, 3 (14%); Calcium channel blocker, 15 (71%); Diuretic, 10 (48%); ASA, 20 (95%); Lipid lowering, 18 (86%); Insulin, 6 (29%); Synthroid, 3 (14%); Antiplatelet, 1 (5%); Aldosterone antagonist, 0 (0%) . Exercise training group: Azathioprine, 4 (18%); Mycophenolate mofetil, 16 (73%); Cyclosporine, 14 (64%); Tacrolimus, 8 (36%); Sirolimus, 2 (9%); Everolimus, 0 (0%); Prednisone, 6 (27%); Agiotensin converting enzyme inhibitor, 13 (59%); Angiotensin II receptor antagonist, 2 (9%); Alpha blocker, 0 (0%); Alpha II agonist, 1 (5%); Beta blocker, 3 (14%); Calcium channel blocker, 11 (50%); Diuretic 8 (36%); ASA, 18 (82%); Lipid lowering, 18 (82%); Insulin, 3 (14%); Synthroid, 4 (18%); Antiplatelet, 1 (5%); Aldosterone antagonist, 1 (5%).

	* number of patients and percentage.
Karapolat 2007	After transplantation, all patients received glucocorticoids, cyclosporine, or tacrolimus, and azathioprine or mycophenolate mofetil. The glucocorticoid regimen consisted of intravenous methyprednisolone (500 mg intraoperatively and 125 mg every 8 hours during the first 24 hours), oral prednisolone (1 mg/kg daily, tapering rapidly from 1 mg/kg per day to 0.2 mg/kg per day within 3 months and then gradually to 0.1 mg/kg per day by 6 months after transplantation, stopped by 2 years if there was no rejection). Rejection was managed by high dose intravenous or oral glucocorticoids, followed by rapid tapering. The precise regimen depended on the severity. Cyclosporine was prescribed at 1 to 3 mg/kg IV for 24 hours. Thereafter the dose was adjusted to maintain a concentration of 200 to 300 ng/mL during the first 6 months. In the case of repeated rejection episodes, cyclosporine was changed to tacrolimus (0.05– 0.15 mg/kg, adjusted to trough levels of 15–20 ng/mL for the first 2 months, 10–15 ng/dL between 2– 6 months and then 8–10 mg/dL). Azathioprine was prescribed at 4 mg/kg per day and then adjusted to maintain the white blood cell count between 4000 to 6000/mm3. Tacrolimus dosage was adjusted to maintain the trough levels between 10 to 15 ng/dL. Mycophenolate mofetil was prescribed at 1000 to 1500 mg BID.
Karapolat 2008	“After transplantation, all patients received glucocorticoids, cyclosporine A/tacrolimus, and azathioprine/mycophenolate mofetil. Theglucocorticoid regimen consisted of intravenous (IV) methyprednisolone (500 mg intraoperatively and 125 mg every 8 h during the first 24 h), oral prednisolone (1 mg/kg daily, tapering rapidly from 1 to 0.2 mg/kg/day within 3 months and then gradually to 0.1 mg/kg/day by 6 months after transplantation, and stopped by 2 years if there is no rejection). Rejection was managed by high dose IV or oral glucocorticoids, followed by rapid tapering; the precise regimen depended upon severity. Cyclosporine A was prescribed at the dose 1–3 mg/kg, IV, for 24 h; the dose was adjusted by serum levels to maintain a concentration of 200–300 ng/ml during the first 6 months. In case of repeated rejection episodes, cyclosporine A was changed to tacrolimus (0.05–0.15 mg/kg, serum level 15–20 ng/ml for the first 2 months, 10–15 ng/dl between 2 and 6 months and then 8–10 mg/dl). Azathioprine was prescribed at the dose 4 mg/kg/day and then adjusted to maintain the white blood cell count between 4,000 and 6,000/mm3. Tacrolimus dosage was adjusted to maintain serum levels between 10 and 15 ng/dl. Mycophenolate mofetil was prescribed 1,000 and 1,500 mg bid.”
Kobashigawa 1999	“All the patients were treated with triple-drug immunosuppression, including cyclosporine, azathioprine, and prednisone. The dosage of prednisone was initially 1 mg per kilogram of body weight per day, given in divided doses, and was gradually de- creased to 0.1 mg per kilogram per day by six months after transplantation. Episodes of cardiac rejection were treated with an oral bolus dose of prednisone and then tapered doses and, for clinically severe rejection, with OKT3 murine monoclonal antibody (muromonab- CD3).

	Exercise training group: Dose of prednisone (mg/day) At 3 months, 12±3; At 6 months, 9±4; Hypertension requiring medication, 8 patients; Calcium-channel blockers or angiotensin-converting–enzyme inhibitors, 8 patients. Control group: Dose of prednisone (mg/day) At 3 months, 14±4; At 6 months, 11±5; Hypertension requiring medication, 11 patients; Calcium-channel blockers or angiotensin-converting–enzyme inhibitors; 11 patients.
Monk-Hansen 2014	Total: Prednisolone, 100/23; Tacrolimus, 17/4; Cyclosporin, 78/18. Exercise training group: Prednisolone, 100/13; Tacrolimus, 15/2; Cyclosporin, 85/11. Control group: Prednisolone, 100/10; Tacrolimus, 20/2; Cyclosporin, 70/7. * Percentage and number of patients.
Nytrøen 2012	Exercise training group: Ciclosporine, 92%; Tacrolimus, 8%; Everolimus, 13%; Mycophenolate, 92%; Azatioprine, 0; Prednisolone, 96%; Beta blocker, 17%; Calcium blocker, 17%; ARB/ACEI, 33%; Diuretics, 29%; Statins, 100%. Control group: Ciclosporine, 80%; Tacrolimus, 13%; Everolimus, 21%; Mycophenolate, 96%; Azatioprine, 4%; Prednisolone, 88%; Beta blocker, 25%; Calcium blocker, 33%; ARB/ACEI, 38%; Diuretics, 33%; 11) Statins, 100%. “All participants were treated according to our immunosuppressive protocol with a calcineurin inhibitor, corticosteroids and mycophenolate mofetil or azathioprine, as well as statins.”
Nytrøen 2019	Protocol for immunosuppressive therapy in supplementary material.

	High intensity interval training group: Cyclosporine, 24 (65%); Tacrolimus, 11(30%); Everolimus, 12(32%); Prednisolone, 37 (100%); Mycophenolate, 34 (92%); Statins, 36 (97%); Beta-Blocker, 9 (24%); Calcium blocker, 8 (22%); ACE inhibitor, 0; ARB inhibitor, 4 (11%); Diuretics, 31 (84%). Moderate intensity continuous training group: Cyclosporine, 31(76%); Tacrolimus, 10(24%); Everolimus, 13 (32%); Prednisolone, 41 (100%); Mycophenolate, 36 (88%); Statins, 41 (100%); Beta-Blocker, 12 (30%); Calcium blocker, 12 (30%); ACEI, 2 (5%); ARB inhibitor, 3 (8%); Diuretics, 32 (78%). * Number of patients and percentage
Pascoalino 2015	Exercise training group: Cyclosporine (77%); Prednisone (58%); Tacrolimus (19%); Azathioprine (26%); Sirolimus (3%); Mycophenolate (64%); Diuretic (39%); ACE inhibitor (42%); Calcium channel blocker (84%); Statin (32%); Sertraline (6%). Control group: Cyclosporine (100%); Prednisone (77%); Tacrolimus (11%); Azathioprine (33%); Sirolimus (0); Mycophenolate (55%); Diuretic (33%); ACE inhibitor (22%); Calcium channel blocker (88%); Statin (33%); Sertraline (11%).
	Study presents institutional protocol for immunosuppressive therapy.
Pierce 2008	Exercise training group: Cyclosporine therapy, 5 (63%); Cyclosporine dose (mg/day) 325.0 ± 127.5; Serum cyclosporine trough levels (ng/ml) 307.3± 23.7; Tacrolimus therapy, 3 (38%); Prednisone therapy, 8 (100%); Prednisone dose (mg/day) 20.6 ± 6.1; Mycophenolate mofetil therapy, 8 (100%); Mycophenolate mofetil dose (mg/day) 2531.30± 986.0; Valgancylovir, 3 (38%); Valgancylovir (mg/day) 612.5 ± 324.7; HMG-CoA reductase inhibitor therapy, 7 (88%); ACEI/ARB therapy, 6 (75%); Insulin, 3 (38%); Calcium channel blocker, 1 (13%). Control group: Cyclosporine therapy, 4 (67%); Cyclosporine dose (mg/day) 356.3 ±51.5; Serum cyclosporine trough levels (ng/ml) 332.3 ± 91.4; Tacrolimus therapy, 2 (33%); Prednisone therapy, 6 (100%); Prednisone dose (mg/day) 23.3 ± 5.2; Mycophenolate mofetil therapy 6 (100%); Mycophenolate mofetil dose (mg/day) 2875.3 ± 250.0; Valgancylovir, 2 (33%); Valgancylovir (mg/day) 850.0 ± 57.7; HMG-CoA reductase inhibitor therapy, 5 (83%); ACEI/ARB therapy, 5 (83%); Insulin, 1 (17%); Calcium channel blocker, 0 (0%).

	* number of patients and percentage; mean and standard deviation.
Rolid 2020	Protocol for immunosuppressive therapy in supplementary material. High intensity interval training group: Cyclosporine, 24 (65%); Tacrolimus, 11(30); Everolimus, 12(32); Prednisolone, 37 (100); Mycophenolate, 34 (92%); Statins, 36 (97%); Beta-Blocker, 9 (24%); Calcium blocker, 8 (22%); ACEI, 0; ARB inhibitor, 4 (11%); Diuretics, 31 (84). Moderate intensity continuous training group: Cyclosporine, 31(76%); Tacrolimus, 10(24%); Everolimus, 13 (32%); Prednisolone, 41 (100%); Mycophenolate, 36 (88%); Statins, 41 (100%); Beta-Blocker, 12 (30%); Calcium blocker, 12 (30%); ACEI, 2 (5%); ARB inhibitor, 3 (8%); Diuretics, 32 (78%). * Number of patients and percentage
Tegtbur 2003	"All patients received a double or triple Immunosuppression with cyclosporine A, prednisolone or azathioprine as well as statins and antihypertensive drugs."
Wu 2008	"The immunosuppressive therapy, which included prednisolone, cyclosporine, azathioprine and FK506, was similar in both groups."

SUPPLEMENTARY MATERIAL 6

Study	Co-interventions
Bernardi 2007	Medication
Braith 1998	Medication "All of the heart transplant recipients participated in postoperative walking programs, but only the training group performed specific resistance exercises."
Braith 2008	Medication
Christensen 2012	Medication
Dall 2014	Medication
Dall 2015	Medication
Haykowsky 2009	Medication
Hermann 2011	Medication
Karapolat 2007	Medication "Prior to the start of the program, all group 2 patients were trained by a physiotherapist how to correctly perform the exercises at home. All exercises taught to Group 2 patients were the same ones as those performed by the patients in Group 1. In addition, however, a walking program was performed by Group 2 patients."
Karapolat 2008	Medication "A walking program was performed by the patients in Group 2 as an aerobic exercise (60%–70% of the pVO_2 and at a level of 13-15 on the Borg scale)." "All patients were given an 8-week program, which consisted of an education component (1 h/week) and an exercise training component. Educational sessions and individual counseling were performed by medical and paramedical staff. The patients received counseling regarding dietary habits, weight management, risk factor modification, and psychosocial issues." "Prior to the start of the program, all of the patients in Group 2 were trained how to correctly perform the exercises by a physiotherapist and they were also instructed to perform the exercises at home."

Kobashigawa 1999	Medication "Before discharge from the hospital, patients in both groups received written guidelines specifying the following exercises to be performed at home: shoulder circles, 10 times forward and 10 times backward; shoulder retraction, 10 slow repetitions of inhaling while bringing the elbows back and exhaling while bringing them forward; trunk twists, 10 times in each direction; side bends, 10 times in each direction; half-squats, 10 to 20 repetitions; and toe raises, 10 to 20 repetitions. Patients also received the following written guidelines for walking: first week after discharge, walk without stopping for 5 to 10 minutes three or four times a day at a comfortable pace; second week, walk 10 to 15 minutes three times a day at a comfortable pace; third week, walk 15 to 20 minutes twice a day at a comfortable pace; fourth week, walk 20 to 30 minutes once a day at a comfortable pace; fifth week, walk 30 to 40 minutes once a day at a comfortable pace; and sixth week, continue walking 30 to 40 minutes every day while increasing the pace."
Monk-Hansen 2014	Medication
Nytröen 2012	Medication "Patients were encouraged to continue any physical activity on their own."
Nytröen 2019	Medication "Each patient was given general advice about lifestyle changes, including a healthy diet, regular exercise, no smoking, and how to avoid infections."
Pascoalino 2015	Medication
Pierce 2008	Medication
Rolid 2020	Medication "Each patient was given general advice about lifestyle changes, including a healthy diet, regular exercise, no smoking, and how to avoid infections." (According *Nytröen, 2019)*
Tegtbur 2003	Medication "Received in addition to medical follow-up care the patients in the intervention group for 12 months rehabilitative at 10 HTX ambulance appointments Services. In addition to the regular medical follow-up care (HTX outpatient clinic), the heart transplant patients received rehabilitation for 10 days and sports medicine services. In psychological and medical consultations, specific motivation and knowledge of health behavior were found as well as for physical activity."
Wu 2008	Medication "To ensure the proper intensity, a supervised education program was provided before homebased training; subjects practiced walking at prescribed speed under physical therapist's supervision until they were familiarized with the speed and confirmed their RPE at 12–14." "The OHT recipients in the National Taiwan University Hospital usually stayed in the hospital for a month and routinely received an inpatient daily physical therapy program. The physical training included functional training and aerobic walking or stationary bike training with an intensity at rating of perceived exertion (RPE). Exercise duration usually could increase up to 30 min per session before discharge. No routine outpatient or monitored home-based exercise program was provided."

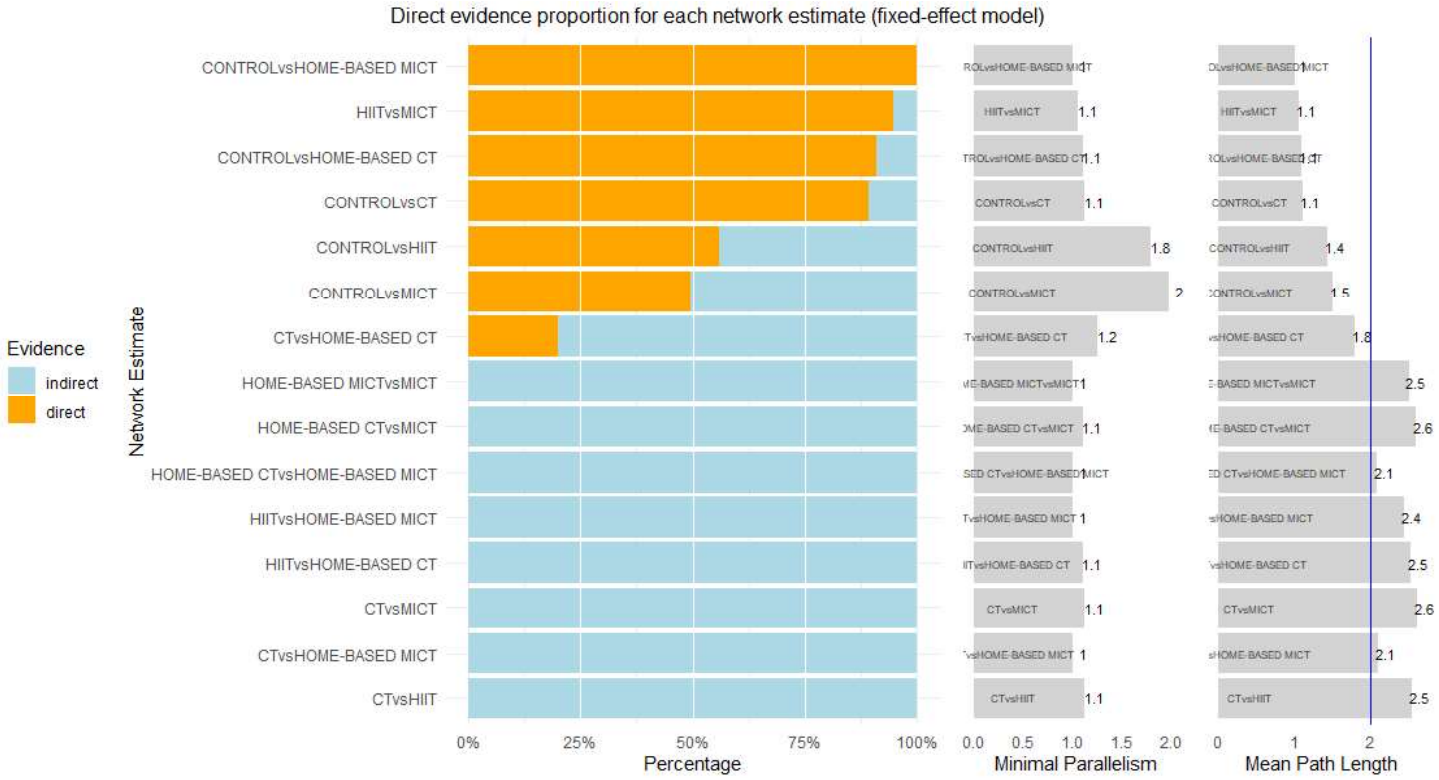
SUPPLEMENTARY MATERIAL 7

Study	DOI	Register on the Clinical Trials	Funding	Potential conflicts of interest
Bernardi 2007	10.1016/j.ijcard.2006.07.032	Unclear	Unclear	Unclear
Braith 1998	10.1097/00005768-199804000-00003	Unclear	Unclear	Unclear
Braith 2005	10.1016/j.amjcard.2005.01.048	Unclear	Unclear	Unclear
Braith 2008	10.1016/j.healun.2007.09.032	Unclear	Yes	Unclear
Christensen 2012	10.1016/j.healun.2011.10.014	NCT01028599	Yes	No
Dall 2014	10.1111/ajt.12873	NCT01914406	Yes	No
Dall 2015	10.1016/j.healun.2015.02.001	NCT01914406	Yes	No
Hermann 2011	10.1111/j.1600-6143.2010.03403.x	NCT01028599	Yes	No
Haykowsky 2009	10.1111/j.1600-6143.2008.02531.x	Unclear	Yes	Unclear
Karapolat 2007	10.1016/j.transproceed.2007.01.079	Unclear	Unclear	Unclear
Karapolat 2008	10.1007/s00392-008-0648-7	Unclear	Unclear	Unclear
Kobashigawa 1999	10.1056/NEJM199901283400404	Unclear	Unclear	Unclear
Monk-Hansen 2014	10.3109/14017431.2013.871058	NCT01028599	Yes	No
Nytrøen 2012	0.1111/j.1600-6143.2012.04221.x	NCT01091194	Yes	No
*Nytrøen 2013**	10.1016/j.healun.2013.06.023	NCT01091194	Yes	No
Nytrøen 2019	10.1161/CIRCULATIONAHA.118.036747	NCT01796379	Yes	No
Pascoalino 2015	10.1016/j.healun.2014.11.013	Unclear	Yes	No
Pierce 2008	10.1097/HJR.0b013e3282f0b63b	Unclear	Yes	Unclear
Rolid 2020	10.1186/s12955-020-01536-4	NCT01796379	Yes	No
*Rustad 2014**	10.1177/2047487312469477	NCT01091194	Yes	No
Tegtbur 2003	10.1007/s00392-003-0968-6	NCT00752336	Unclear	Unclear
Wu 2008	10.1159/000119695	Unclear	Unclear	Unclear

SUPPLEMENTARY MATERIAL 8

Study	Treatment A	n	Pre	Post	Change	Treatment B	n	Pre	Post	Change	TE±seTE
*Bernardi 2007**	HOME-BASED MICT	13	14.93±4.43	19.61±2.34	4±6.98	CONTROL	11	14.33±4.11	15.60±5.83	1.27±7.13	3.41±2.55
*Braith 2008**	MICT	9	15.4±4.3	19.4±5.5	4.9±2.7	CONTROL	7	16.2±5.2	16.8±2.8	0.6±5.91	3.40±3.22
Dall 2014	HIIT	16	23.2±6.9	28.1±8.1	3.43±3.3	MICT	16	23.0±6.6	25.6±6.6	2.6±2.2	2.30±0.87
Haykowsky 2009	CT	22	21.2±7.3	24.7±8.8	4.4±9.06	CONTROL	19	18.2±5.9	18.2±5.3	0.04±2.2	3.39±0.86
*Hermann 2011**	HIIT	14	23.9±6.7	28.3±6.1	2.8±5.52	CONTROL	13	24.6±5.0	23.4±5.7	-1.2±7.58	5.60±3.20
*Karapolat 2007**	CT	15	16.73±3.91	19.53±3.89	4.4±7.54	HOME-BASED CT	13	20.12±4.40	19.48±4.53	-0.64±6.32	3.44±2.25
*Kobashigawa 1999**	CT	14	9.2±5.07	13.6±5.57	3.2±7.64	CONTROL	13	10.4±5.15	12.3±5.01	1.9±7.19	2.50±2.83
*Nytroen 2012**	HIIT	24	27.7±5.5	30.9±5.3	4.83±4.09	CONTROL	24	28.5±7.0	28.0±6.7	-0.5±9.69	3.70±2.51
Nytroen 2019	HIIT	37	19.5±4.3	24.4±6.5	2.2±8.69	MICT	41	21.3±5.3	24.4±6.7	3±5.78	1.83±1.12
*Pascoalino 2015**	MICT	31	21±5.56	23.2±6.68	1.3±5.94	CONTROL	9	20.8±5.4	20.1±4.5	-0.7±7.03	2.90±2.81
*Tegtbur 2003**	HOME-BASED MICT	20	18.8±4.2	20.1±4.2	1±2.5	CONTROL	12	19.3±4.5	18.5±2.8	-0.8±5.3	2.10±2.02
Wu 2008	HOME-BASED CT	14	12.1±2.7	13.2±3.9	4±6.98	CONTROL	23	13.7±3.3	13.2±3.7	-0.5±1.8	1.50±0.76

SUPPLEMENTARY MATERIAL 9

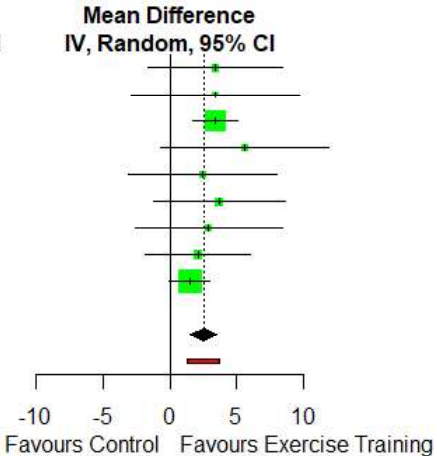


SUPPLEMENTARY MATERIAL 10

Exercise training *versus* control

Study	Exercise Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Bernardi 2007	4.68	5.01	13	1.27	7.13	11	3.8%	3.41 [-1.61; 8.43]
Braith 2008	4.00	6.98	9	0.60	5.91	7	2.4%	3.40 [-2.92; 9.72]
Haykowsky 2009	3.43	3.30	22	0.04	2.20	19	33.1%	3.39 [1.69; 5.09]
Hermann 2011	4.40	9.06	14	-1.20	7.58	13	2.4%	5.60 [-0.68; 11.88]
Kobashigawa 1999	4.40	7.54	14	1.90	7.19	13	3.1%	2.50 [-3.06; 8.06]
Nytroen 2012	3.20	7.64	24	-0.50	9.69	24	3.9%	3.70 [-1.24; 8.64]
Pascoalino 2015	2.20	8.69	31	-0.70	7.03	9	3.1%	2.90 [-2.62; 8.42]
Tegtbur 2003	1.30	5.94	20	-0.80	5.30	12	6.0%	2.10 [-1.87; 6.07]
Wu 2008	1.00	2.50	14	-0.50	1.80	23	42.2%	1.50 [0.00; 3.00]
Total (95% CI)			**161**			**131**	**100.0%**	**2.54 [1.56; 3.51]**
Prediction interval								**[1.36; 3.72]**

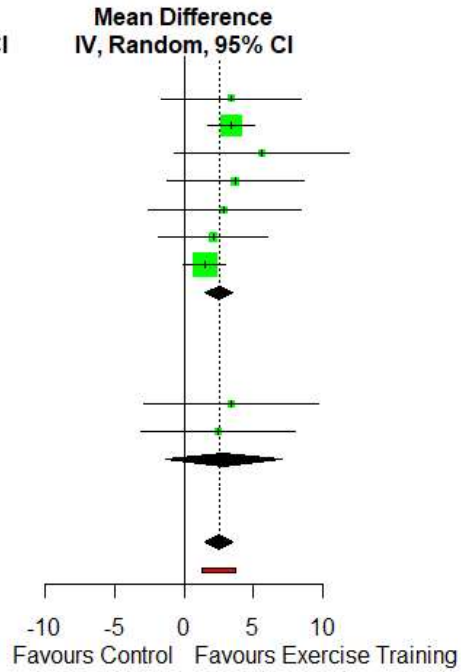
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.18$, df = 8 (P = 0.84); $I^2 = 0\%$
Test for overall effect: Z = 5.10 (P < 0.01)



Subgroup analysis between recent *versus* late heart transplant recipients

Study or Subgroup	Exercise Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Post-HTx time = At least 6 months								
Bernardi 2007	4.68	5.01	13	1.27	7.13	11	3.8%	3.41 [-1.61; 8.43]
Haykowsky 2009	3.43	3.30	22	0.04	2.20	19	33.1%	3.39 [1.69; 5.09]
Hermann 2011	4.40	9.06	14	-1.20	7.58	13	2.4%	5.60 [-0.68; 11.88]
Nytroen 2012	3.20	7.64	24	-0.50	9.69	24	3.9%	3.70 [-1.24; 8.64]
Pascoalino 2015	2.20	8.69	31	-0.70	7.03	9	3.1%	2.90 [-2.62; 8.42]
Tegtbur 2003	1.30	5.94	20	-0.80	5.30	12	6.0%	2.10 [-1.87; 6.07]
Wu 2008	1.00	2.50	14	-0.50	1.80	23	42.2%	1.50 [0.00; 3.00]
Total (95% CI)			**138**			**111**	**94.5%**	**2.52 [1.51; 3.52]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.11$, df = 6 (P = 0.66); $I^2 = 0\%$								
Post-HTx time = Less than 6 months								
Braith 2008	4.00	6.98	9	0.60	5.91	7	2.4%	3.40 [-2.92; 9.72]
Kobashigawa 1999	4.40	7.54	14	1.90	7.19	13	3.1%	2.50 [-3.06; 8.06]
Total (95% CI)			**23**			**20**	**5.5%**	**2.89 [-1.28; 7.07]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.04$, df = 1 (P = 0.83); $I^2 = 0\%$								
Total (95% CI)			**161**			**131**	**100.0%**	**2.54 [1.56; 3.51]**
Prediction interval								**[1.36; 3.72]**

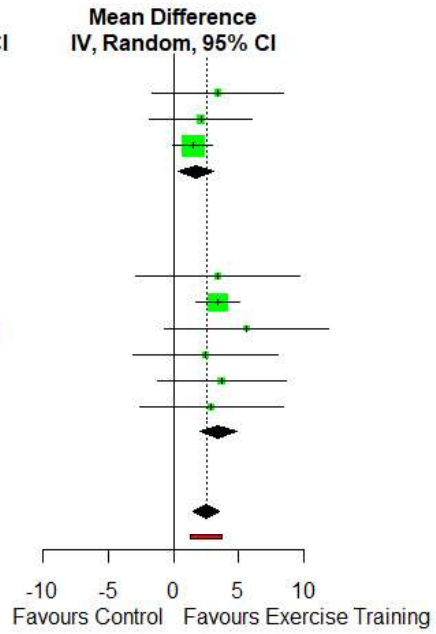
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.18$, df = 8 (P = 0.84); $I^2 = 0\%$
Residual heterogeneity: $Tau^2 = NA$; $Chi^2 = 4.15$, df = 7 (P = 0.76); $I^2 = 0\%$
Test for overall effect: Z = 5.10 (P < 0.01)



Subgroup analysis between home-based *versus* center-based exercise training

Study or Subgroup	Exercise Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Exercise training = Home-based								
Bernardi 2007	4.68	5.01	13	1.27	7.13	11	3.8%	3.41 [-1.61; 8.43]
Tegtbur 2003	1.30	5.94	20	-0.80	5.30	12	6.0%	2.10 [-1.87; 6.07]
Wu 2008	1.00	2.50	14	-0.50	1.80	23	42.2%	1.50 [0.00; 3.00]
Total (95% CI)			**47**			**46**	**52.0%**	**1.71 [0.36; 3.06]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.55$, df = 2 (P = 0.76); $I^2 = 0\%$								
Exercise training = Center-based								
Braith 2008	4.00	6.98	9	0.60	5.91	7	2.4%	3.40 [-2.92; 9.72]
Haykowsky 2009	3.43	3.30	22	0.04	2.20	19	33.1%	3.39 [1.69; 5.09]
Hermann 2011	4.40	9.06	14	-1.20	7.58	13	2.4%	5.60 [-0.68; 11.88]
Kobashigawa 1999	4.40	7.54	14	1.90	7.19	13	3.1%	2.50 [-3.06; 8.06]
Nytroen 2012	3.20	7.64	24	-0.50	9.69	24	3.9%	3.70 [-1.24; 8.64]
Pascoalino 2015	2.20	8.69	31	-0.70	7.03	9	3.1%	2.90 [-2.62; 8.42]
Total (95% CI)			**114**			**85**	**48.0%**	**3.44 [2.03; 4.85]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.61$, df = 5 (P = 0.99); $I^2 = 0\%$								
Total (95% CI)			**161**			**131**	**100.0%**	**2.54 [1.56; 3.51]**
Prediction Interval								**[1.36; 3.72]**

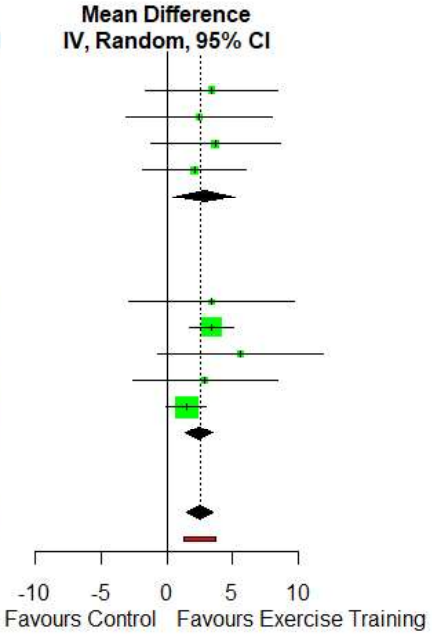
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.18$, df = 8 (P = 0.84); $I^2 = 0\%$
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 1.17$, df = 7 (P = 0.99); $I^2 = 0\%$
Test for overall effect: Z = 5.10 (P < 0.01)



Subgroup analysis between short *versus* long term exercise training

Study or Subgroup	Exercise Training Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Exercise training follow-up = At least 6 months								
Bernardi 2007	4.68	5.01	13	1.27	7.13	11	3.8%	3.41 [-1.61; 8.43]
Kobashigawa 1999	4.40	7.54	14	1.90	7.19	13	3.1%	2.50 [-3.06; 8.06]
Nytroen 2012	3.20	7.64	24	-0.50	9.69	24	3.9%	3.70 [-1.24; 8.64]
Tegtbur 2003	1.30	5.94	20	-0.80	5.30	12	6.0%	2.10 [-1.87; 6.07]
Total (95% CI)			**71**			**60**	**16.8%**	**2.84 [0.46; 5.22]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 0.31$, df = 3 (P = 0.96); $I^2 = 0\%$								
Exercise training follow-up = Less than 6 months								
Braith 2008	4.00	6.98	9	0.60	5.91	7	2.4%	3.40 [-2.92; 9.72]
Haykowsky 2009	3.43	3.30	22	0.04	2.20	19	33.1%	3.39 [1.69; 5.09]
Hermann 2011	4.40	9.06	14	-1.20	7.58	13	2.4%	5.60 [-0.68; 11.88]
Pascoalino 2015	2.20	8.69	31	-0.70	7.03	9	3.1%	2.90 [-2.62; 8.42]
Wu 2008	1.00	2.50	14	-0.50	1.80	23	42.2%	1.50 [0.00; 3.00]
Total (95% CI)			**90**			**71**	**83.2%**	**2.48 [1.41; 3.55]**
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.79$, df = 4 (P = 0.44); $I^2 = 0\%$								
Total (95% CI)			**161**			**131**	**100.0%**	**2.54 [1.56; 3.51]**
Prediction interval								**[1.36; 3.72]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 4.18$, df = 8 (P = 0.84); $I^2 = 0\%$
Residual heterogeneity: Tau^2 = NA; $Chi^2 = 4.10$, df = 7 (P = 0.77); $I^2 = 0\%$
Test for overall effect: Z = 5.10 (P < 0.01)



Artigo 1

REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO - PARTE I

Juliana Beust de Lima,[1,2] Filipe Ferrari,[1,2] Ricardo Stein[1,2,3]

1. Grupo de Pesquisa em Cardiologia do Exercício do Hospital de Clínicas de Porto Alegre (CardioEx-HCPA)

2. Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares

3. Professor Adjunto do Serviço de Fisiatria e Reabilitação do Hospital de Clínicas de Porto Alegre da Universidade Federal do Rio Grande do Sul (HCPA-UFRGS)

O transplante cardíaco (Txc) é o tratamento de escolha para pacientes com insuficiência cardíaca (IC) refratária que permanecem com sintomas graves mesmo em uso de todo arsenal medicamentoso disponível e/ou realização de procedimentos cirúrgicos. O Txc tem como objetivo promover a melhora na qualidade de vida, assim como sobrevida nessa população.[1,2]

Nos últimos anos houve avanços significativos no que diz respeito ao Txc, com surgimento de novas técnicas cirúrgicas e desenvolvimento de drogas imunossupressoras mais eficientes. No Brasil, houve um crescimento substancial no número de procedimentos, sendo realizados 380 Txc em 2017. Até março de 2018, 84 corações já haviam sido transplantados no Brasil.[3] Os receptores são capazes de retornar ao trabalho e terem vida normal, vivendo com nenhum ou apenas sintomas mínimos.[4] A taxa de sobrevida no primeiro ano é estimada em 90% e, em cinco anos, cerca de 70%.[5]

Embora o Txc melhore significativamente a capacidade funcional dos pacientes, o consumo de oxigênio de pico ($\dot{V}O_2$ pico) ainda se encontra reduzido quando comparado ao de indivíduos saudáveis pareados por idade.[6,7] Alguns fatores podem explicar tais

fatos: 1) imediatamente no período pós-transplante, o aloenxerto apresenta ausência de inervação simpática e parassimpática (denervação autonômica), provocando aumento da frequência cardíaca (FC) de repouso, atenuando a sua elevação natural como resposta ao exercício e prejudicando a recuperação após esforço;[7,8] 2) disfunção muscular esquelética, na qual a terapia imunossupressora associada à IC prévia exercem papel de destaque;[9] 3) função vascular e diastólica comprometidas.[10]

Na fase aguda do exercício, o aumento do débito cardíaco depende fundamentalmente do mecanismo de Frank-Starling.[11,12] Além disso, durante o exercício progressivo, ocorre aumento das concentrações de catecolaminas circulantes,[10] as quais começam a reduzir lentamente após o término do exercício, o que justifica uma lenta recuperação da FC após o esforço.[13] Em concomitância, a imunossupressão em excesso pode predispor a um maior risco de complicações,[14] e os pacientes transplantados não raramente podem cursar com desenvolvimento de hipertensão arterial sistêmica, diabetes mellitus e coronariopatia.[15] Por sua vez, o treinamento físico é conhecido como uma ferramenta terapêutica de excelência para o manejo dessas doenças crônicas[16,17] e também eficaz na otimização no controle autonômico.[7,18]

O treinamento físico após o Txc contribui no aumento do $\dot{V}O_2$ pico, na melhora do controle hemodinâmico, força muscular e densidade mineral óssea,[19-21] podendo assim, inclusive, melhorar o prognóstico nesta população.[22] Embora existam inúmeras possibilidades de prescrição de treinamento, o método preconizado permanece sendo o exercício aeróbico, que pode ser realizado de forma contínua ou intervalada e em diferentes intensidades[23] e, sempre que possível, associado aos exercícios resistidos.[24]

Neste e nos dois próximos números da Revista do DERC, apresentaremos uma visão detalhada sobre os cuidados na prescrição e os benefícios das diversas modalidades de treinamento físico em pacientes pós-Txc, entre elas o treinamento intervalado de alta intensidade (TIAI), muito discutido ultimamente. Nesta edição da revista, versaremos sobre a avaliação pré-participação e a prescrição do treinamento pós-TxC. No próximo número serão contemplados diversos aspectos relacionados ao treinamento físico pós-Txc (Parte II). Finalmente, no número seguinte, as recomendações e as considerações finais serão apresentadas (parte III).

Avaliação pré-participação e prescrição do treinamento pós-Txc

A atuação de uma equipe multidisciplinar é desejável no processo de reabilitação cardiovascular. No que tange ao treinamento físico, o conhecimento de profissionais com diferentes formações possibilita a adequada avaliação e prescrição desta importante modalidade terapêutica. Assim como nas demais condições clínicas, pacientes pós-Txc devem ser adequadamente avaliados. Para isso, a anamnese é primordial, seguida por exame físico, eletrocardiograma de repouso de 12 derivações, ecocardiograma Doppler em cores e por um teste de exercício, permanecendo o teste cardiopulmonar de exercício (TCPE) como o método padrão ouro na avaliação da capacidade funcional. Este exame deve ser realizado por um médico cardiologista capacitado e certificado; é útil na avaliação das respostas clínicas, eletrocardiográficas e respiratórias durante o exercício. A avaliação do fisiatra e/ou fisioterapeuta prévia à realização dos exercícios auxilia na identificação de possíveis limitações osteomioarticulares que podem estar presentes em muitos pacientes. Tais condições, quando identificadas, devem ser tratadas e levadas em consideração na prescrição do treinamento. O fisioterapeuta e o profissional de educação física trabalham em conjunto na prescrição e orientação dos exercícios, seguindo os limites de segurança recomendados pelo médico responsável pelo caso.[24,25]

A impossibilidade da realização do TCPE não deve ser um impedimento para a prática do exercício. Na ausência deste exame, sugere-se a realização de um teste ergométrico.[23] Quando nem mesmo este estiver disponível, o Teste de Caminhada de 6 minutos poderá auxiliar na avaliação clínica durante o exercício, além de fornecer um parâmetro de comparação da capacidade funcional no decorrer do treinamento. [26,27] A determinação de zonas alvo de treinamento é necessária, visando à prescrição segura e otimizada do exercício.[23] No entanto, tendo em vista a resposta cronotrópica ainda comprometida,[28] a prescrição baseada nos percentuais da FC máxima ou na FC nos limiares, na maioria das vezes, não é possível nas primeiras sessões de treinamento, especialmente nos pacientes com cirurgia recente. No entanto, podem ser úteis conforme se observa melhora na resposta autonômica.[7] Por este motivo, a contínua avaliação do comportamento da FC durante o exercício e na recuperação se torna de suma importância. Quando um TCPE for viável, a prescrição do exercício aeróbico pode ser baseada na sobrecarga (velocidade e inclinação) atingida nos limiares ventilatórios ou nos

percentuais estabelecidos do $\dot{V}O_2$ pico. Outra estratégia simples e viável é a avaliação da percepção subjetiva do esforço, através da escala de Borg.[23,29,30] Neste sentido, o empenho da equipe multidisciplinar em educar o paciente em relação à percepção de esforço e manifestações de sintomas é de grande valia.

Enquanto Diretrizes nacionais e internacionais estabelecem métodos de avaliação e parâmetros de segurança para prescrição do exercício aeróbico,[23-25,29,32] menos se discute sobre os exercícios resistidos. Os métodos tradicionalmente utilizados para a avaliação e prescrição precisa dos exercícios são os testes de carga. No entanto, atenção especial de ser dada na aplicação destes protocolos em pacientes pós-Txc, principalmente naqueles pós-procedimento recente, uma vez que a condição hemodinâmica cardíaca e neuromotora ainda estão bastante alteradas, assim como o esterno em processo de cicatrização. A segurança na aplicação destes testes carece de investigações clínicas. Uma alternativa é o teste de sentar e levantar da cadeira em trinta segundos.[32] Este teste foi validado em idosos ativos e se mostrou razoavelmente confiável em fornecer um indicador sobre a força de membros inferiores. Já é bastante utilizado em centros de reabilitação e em estudos científicos nas quais foram avaliadas diferentes condições clínicas.[33-35] No entanto, julgamos ser necessária a realização de estudos fisiológicos que avaliem as repercussões hemodinâmicas do protocolo em pacientes pós-Txc para que esse possa ser utilizado de maneira mais segura e rotineira.

A prescrição do exercício será pautada nas recomendações específicas de cada uma das quatro fases da reabilitação cardiovascular.[24] No entanto, vale salientar que o profissional deve sempre considerar os princípios da individualidade biológica e da especificidade, adaptando o treinamento conforme as possibilidades e necessidades individuais.[36] Pacientes pós-Txc podem apresentar múltiplas comorbidades, e também por esse motivo o conhecimento da repercussão do exercício nos diferentes sistemas fisiológicos é requerido aos profissionais que guiarão as sessões de treinamento.[7]

Em levantamento realizado nos Estados Unidos, foi evidenciado que 36% dos receptores acabam sendo hospitalizados ao longo do primeiro ano pós-Txc e 61% dentro de um período de quatro anos, sendo os motivos mais comuns complicações e infecções relacionadas ao procedimento.[37,38] Esta alta prevalência alerta sobre a importância da supervisão contínua dos pacientes ao longo do treinamento, uma vez que nessas condições as sessões devem ser, mesmo que temporariamente, interrompidas. Da mesma

forma, alguns autores sugerem que os pacientes não devam realizar exercício físico durante o período de administração de terapia com pulsos esteroides,[23] assim como não se justifica a realização da atividade nos dias de biópsia.

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Artigo 2

REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE II: TREINAMENTOFÍSICO PÓS-TRANSPLANTE CARDÍACO

Juliana Beust de Lima,[1,2] Filipe Ferrari,[1,2] Ricardo Stein[1,2,3]

1. Grupo de Pesquisa em Cardiologia do Exercício do Hospital de Clínicas de Porto Alegre (CardioEx-HCPA)

2. Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares

3. Professor Adjunto do Serviço de Fisiatria e Reabilitação do Hospital de Clínicas de Porto Alegre da Universidade Federal do Rio Grande do Sul (HCPA-UFRGS)

A definição de alguns conceitos e o conhecimento dos princípios que norteiam a prescrição do treinamento físico é essencial. O termo "atividade física" caracteriza-se por qualquer movimento corporal produzido pelos músculos esqueléticos que resulte em gasto energético acima dos níveis de repouso; ao passo que "exercício físico" é uma atividade física planejada e estruturada com o objetivo de melhorar ou manter alguma valência física, sendo que as melhores adaptações fisiológicas ocorrem na realização de sessões acumuladas dentro de um treinamento periodizado.[1,2] Periodização, por sua vez, é o manejo das variáveis do treinamento visando a supercompensação como resposta ao estímulo estressor.[3] Tais variáveis se referem à frequência, intensidade, duração, tipo e a combinação destes componentes.[4] Também muito importante a serem considerados são os princípios do treinamento físico: individualidade biológica, sobrecarga, especificidade e reversibilidade.[5]

Nesse contexto, o treinamento físico é o componente central da reabilitação cardiovascular. Concomitante ao tratamento farmacológico, mostra-se seguro e eficaz em melhorar a capacidade funcional em pacientes pós-transplante cardíaco (Txc).[6] Capacidade funcional, por sua vez, é medida objetivamente pelo consumo de oxigênio de

pico ($\dot{V}O_2$ pico), um poderoso marcador prognóstico nessa população, estando inversamente associada à morbidade e mortalidade.[7,8]

A Diretriz Sul-Americana de Prevenção e Reabilitação Cardiovascular[8] destaca a importância da realização de exercícios durante a internação e após a alta hospitalar. O treinamento aeróbico é o preconizado, devendo ser complementado pelo resistido a partir da sexta semana pós-Txc. Neste documento, é enfatizado que se a condição clínica do paciente permitir, a intensidade do exercício aeróbico pode aumentar gradualmente de moderada a alta ao longo do treinamento, a fim de otimizar as adaptações e benefícios. Neste sentido, programas que incluíram o treinamento intervalado, até mesmo de alta intensidade, mostraram bons resultados nestes indivíduos.[1]

Diferentes metodologias de treinamento vêm sendo estudadas de forma isolada e têm se mostrado eficazes na promoção da saúde cardiovascular nos indivíduos em reabilitação.[6,8] Em pacientes pós-Txc a maioria dos estudos avaliou o efeito do treinamento contínuo de moderada intensidade. No estudo pioneiro de Richard et al.,[9] os pesquisadores observaram que em um período de 46 meses pós-Txc, pacientes que realizaram treinamento aeróbico – em média 4 vezes por semana durante três anos – apresentaram capacidade funcional e função cronotrópica semelhantes às verificadas em indivíduos saudáveis. Tal experimento lançou a hipótese do efeito favorável do exercício e deu embasamento para ensaios clínicos randomizados posteriores.

Metanálise recente da Cochrane,[10] que reuniu nove ensaios clínicos randomizados, totalizando 284 pacientes, comparou o efeito do treinamento físico com cuidados usuais em pacientes pós-Txc.[10] Destes, oito compararam o efeito do treinamento aos cuidados usuais e um comparou o treinamento contínuo de moderada intensidade (TCMI) com o treinamento intervalado de alta intensidade (TIAI). Todos os estudos incluíram um grupo pequeno de pacientes estáveis clinicamente e as intervenções duraram em média 12 semanas. O treinamento aeróbico, através de caminhada, corrida ou ciclismo, foi o de escolha em todos os estudos, sendo que nos experimentos de Haykowsky et al.11 e Kobashigawa et al.[12] esse tipo de exercício foi complementado pelo resistido, em uma metodologia denominada treinamento combinado. A prescrição do treinamento diferiu muito entre os estudos, com uma frequência semanal variando de uma a cinco sessões, duração de 28 a 50 minutos e intensidade controlada por diferentes parâmetros. Seis estudos que avaliaram morte cardiovascular e por todas as causas não

evidenciaram nenhuma ocorrência destes desfechos durante o período de seguimento. Sete ensaios avaliaram eventos adversos, ocorrendo apenas no estudo de Nytrøen al.,[13] que relatou um caso de infarto agudo do miocárdio no grupo controle, mas nenhum caso no grupo intervenção, reforçando a segurança do treinamento quando este é bem controlado. Em relação à capacidade funcional foi evidenciado um aumento de 2,49 $mL.kg^{-1}.min^{-1}$ (IC 95%: 1,63 $mL.kg^{-1}.min^{-1}$ – 3,36 $mL.kg^{-1}.min^{-1}$) nos grupos que realizaram treinamento, em relação aos randomizados para cuidados usuais.

A intensidade do treinamento está diretamente associada à magnitude das adaptações cardiovasculares.[14] Contudo, para uma otimizada e segura prescrição do exercício em programas de reabilitação, deve-se considerar a duração, intensidade e os períodos de descanso dentro de cada sessão.[6] O TIAI alterna períodos mais intensos com momentos de recuperação passiva ou ativa, possibilitando que alta intensidade de exercício seja mantida por mais tempo e, consequentemente, gerando um estímulo maior para adaptações fisiológicas centrais e periféricas. Em pacientes com IC com fração de ejeção reduzida, Wisløff et al.[15] demonstraram que o TIAI foi superior ao TCMI em promover a melhora na capacidade funcional e em diferentes parâmetros cardiovasculares. Posteriormente, outros ensaios clínicos foram realizados e meta-analisados. No que tange ao efeito do TIAI sobre a capacidade funcional, a superioridade do método em relação ao TCMI foi confirmada.[16] No entanto, em publicação recente (estudo multicêntrico Smartex-HF), ambos os métodos foram igualmente eficazes em promover o aumento no VO_2 pico.[17]

Menos se sabe sobre o efeito do TIAI em pacientes pós-Txc. No entanto, os resultados observados são motivadores. Em um estudo crossover, Dall et al.[18] verificaram efeito superior do método intervalado em relação ao TCMI no $\dot{V}O_2$ pico (2,3 $mL.kg^{-1}.min^{-1}$; IC 95%: 1,1 $mL.kg^{-1}.min^{-1}$ – 3,4 $mL.kg^{-1}.\ min^{-1}$) e na qualidade de vida. Recente metanálise[1] reuniu três ensaios clínicos randomizados que compararam o TIAI (blocos intensos: 80 a 100% do VO_2 pico ou 85 a 95% da frequência cardíaca máxima) aos cuidados usuais. Pacientes pós-Txc que realizaram TIAI apresentaram aumento no VO_2 pico (4,45 $mL.kg^{-1}.min^{-1}$; IC 95%: 2,15 $mL.kg^{-1}.min^{-1}$ – 6,75 $mL.kg^{-1}.min^{-1}$), frequência cardíaca máxima e pressão arterial máxima após períodos de intervenção que variaram de oito a 12 semanas, sendo realizadas três a cinco sessões semanais.

Um grupo de pesquisadores escandinavos planeja testar se o TIAI também é viável e seguro em receptores recentemente transplantados, e se o efeito desta intervenção no VO_2 pico é superior ao efeito do TCMI. Será um estudo multicêntrico que incluirá 120 pacientes acompanhados por pelo menos um ano, sendo um subgrupo seguido até três anos. O experimento visa avaliar se a capacidade funcional apresentará aumento sustentado, assim como averiguar se as complicações tardias serão diminuídas nesse período de seguimento. Os autores acreditam que se o TIAI confirmar ser seguro, eficaz e até mesmo superior ao TCMI, pacientes pós-Txc poderão ser beneficiados por esta estratégia de treinamento. Diferenciais deste experimento serão a reabilitação descentralizada e em cooperação com os serviços primários de saúde, além da população ser de pacientes com oito a 12 semanas pós-Txc.[19]

É sabido que alguns dos efeitos adversos comuns ao uso de glicocorticoides após o Txc são atrofia e fraqueza musculares. Em 1998, Braith et al.[20] estudaram pela primeira vez o efeito do treinamento resistido na miopatia induzida por glicocorticoide em receptores de Txc. Um grupo realizou treinamento e foi comparado com um grupo controle, sem nenhum tipo de treinamento. Após seis meses, apesar de ambos terem apresentado aumento na força muscular do quadríceps (medido com teste de uma repetição máxima dinâmico) e força dos extensores lombares (avaliada pela extensão lombar isométrica em sete posições), houve um aumento até seis vezes maior no grupo treinado.

O treinamento resistido também parece ser uma importante terapêutica para melhoria do metabolismo ósseo. Após o Txc, os pacientes não raramente apresentam perda óssea significativa na cabeça do fêmur e perda óssea mineral total. Nesse sentido, pacientes foram arrolados para treinamento resistido após dois meses da realização do Txc. O treinamento de força se mostrou capaz de restaurar a densidade mineral óssea a níveis pré-transplante.[21] Dessa forma, exercícios de fortalecimento muscular devem ser incorporados nos programas de treinamento para reverter, ao menos em parte, esses fatores.

Haykowsky et al.[22] descreveram melhoras significativas no $\dot{V}O_2$ pico de pacientes pós-Txc. Após 12 semanas de treinamento resistido e aeróbico combinados, houve um aumento de 3,11 $mL.kg^{-1}.min^{-1}$ (IC 95: 1,2 $mL.kg^{-1}.min^{-1}$ – 5,0 $mL.kg^{-1}.min^{-1}$). Kobashigawa et al.[23] estudaram 27 pacientes pós-Txc, os quais foram submetidos a uma

combinação de treinamento aeróbico, resistido e de flexibilidade durante seis meses versus grupo controle (terapia não estruturada em casa). A prescrição era feita indivualmente. A duração e a intensidade das sessões de exercícios aeróbicos tiveram como meta o mínimo de 30 minutos de exercício contínuo de intensidade moderada em bicicleta estacionária. O grupo intervenção apresentou um aumento médio de 4,4 mL. $kg^{-1}.min^{-1}$ vs 1,9 $ml.kg^{-1}.min^{-1}$ no grupo controle. Esses dados fornecem informações valiosas da importância de ambos os tipos de treinamento para essa população.

Estudos prévios demonstraram que os programas domiciliares de reabilitação cardíaca são seguros e efetivos.[24] O American College of Cardiology recomenda a reabilitação cardíaca domiciliar como um substituto para reabilitação realizada em centros para pacientes de baixo risco, considerado este tratamento classe de recomendação 1 com nível de evidência A.[25] A reabilitação pós-Txc com exercícios realizados em casa pode representar uma excelente alternativa para os pacientes, dado o baixo custo e o fato de serem acessíveis à maioria dos pacientes após o procedimento.

Wu et al.[26] conduziram um estudo prospectivo e randomizado para avaliar o efeito de um programa de exercícios domiciliares durante dois meses em 37 pacientes pós- Txc. O grupo controle manteve o estilo de vida habitual durante o período de estudo. Os indivíduos do grupo intervenção realizaram um programa de exercício que englobou cinco minutos de aquecimento, exercícios de fortalecimento de membros superiores e inferiores, 15 a 20 minutos de exercício aeróbico em uma intensidade de 60 a 70% do $\dot{V}O_2$ pico, além de cinco minutos de desaquecimento. O treinamento era realizado por pelo menos três vezes na semana. Para garantir a intensidade correta, foi fornecido um programa de educação supervisionado antes do treinamento. Ao final de dois meses, os pacientes melhoraram força e resistência muscular, índice de fadiga e qualidade de vida no domínio físico. Através do teste cardiopulmonar de exercício (TCPE), foi observado aumento na carga de trabalho. No entanto, não houve aumento no $\dot{V}O_2$ pico, o que pode ser resultado do curto período de seguimento ou de características específicas da prescrição do treinamento. Corroborando com esses resultados, aplicando treinamento físico domiciliar cinco vezes por semana durante seis meses, através de protocolo de treinamento aeróbico com a mesma intensidade, Bernardi et al.[27] verificaram a segurança e melhora no $\dot{V}O_2$ pico, carga de trabalho e pressão arterial (sistólica e diastólica) de indivíduos pós-Txc. Além disso, verificaram sinais de reinervação simpática cardíaca e

restauração da sensibilidade à modulação autonômica nas artérias. Por outro lado, nenhuma alteração foi observada no grupo controle. Esses achados sugerem que o exercício físico realizado em casa pode melhorar a atividade nervosa autonômica tanto no coração quanto nos vasos sanguíneos periféricos, o que poderia contribuir para a melhora no desempenho físico nesses sujeitos.

Mesmo naqueles pacientes após longo período pós-Txc (acima de cinco anos), a reabilitação baseada em exercício físico melhora a capacidade funcional. Vinte e um pacientes foram instruídos a realizar um programa de treinamento físico por um ano em bicicleta ergométrica domiciliar, enquanto nove pacientes serviram como controles. Para garantir o adequado controle, os pacientes receberam um cartão inteligente, programado para um aquecimento de seis minutos e uma carga de trabalho constante durante 20 minutos. Caso a frequência cardíaca (FC) do participante excedesse a intensidade prescrita, o cartão reduzia a intensidade de treinamento. Ao final de 12 meses, houve modesta melhora no $\dot{V}O_2$ pico.[28] Ou seja, mesmo após um longo período de Txc, o treinamento físico regular deve ser realizado para evitar a diminuição acelerada da capacidade de exercício causada pelo tratamento imunossupressor e pela inatividade física.

Karapolat et al.[29] compararam os efeitos de programas de exercícios domiciliares e hospitalares sobre a capacidade de exercício e variáveis cronotrópicas em 28 pacientes pós-Txc, encontrando melhoras significativas no VO_2 pico e na FC de reserva apenas no grupo que realizou treinamento em um centro de reabilitação cardíaca; não foram observadas mudanças significativas em qualquer desses parâmetros no grupo que realizou treinamento domiciliar. Neste estudo, todos os pacientes receberam aconselhamento sobre hábitos alimentares, controle de peso, modificação de fatores de risco e questões psicossociais. As sessões de exercício duraram em média uma hora e meia (três vezes por semana, durante dois meses) e incluíram exercícios de flexibilidade, exercícios aeróbicos, exercícios de fortalecimento, exercícios de respiração e exercícios de relaxamento.

De forma surpreendente, alguns pacientes podem apresentar níveis de condicionamento altíssimos, participando de esportes altamente competitivos. Por exemplo, há evidências da participação de transplantados desde provas de resistência de alto desempenho,[30] prova de Ironman,[31] à escalada nos picos mais altos do mundo.[32] Em

um desses estudos,[31] o transplantado completou em 2008, aos 49 anos de idade, uma prova de Ironman no Canadá, 22 anos após a cirurgia. Essa prova é conhecida como

um dos eventos mais extenuantes para o corpo humano em um único dia, englobando 3,8 km de natação, 180 km de ciclismo e 42,2 km de corrida. Por outro lado, em 25 de agosto, Kelly Perkins, uma americana, surpreendeu os montanhistas e os médicos ao se tornar a primeira pessoa pós-Txc a escalar a montanha Matterhorn, localizada na fronteira da Suíça com a Itália.[32] Surpreendentemente, ela escalou 4.478 metros. Dessa forma, estudos posteriores devem avaliar de forma mais precisa a possibilidade de que mais pacientes após Txc possam se engajar em competições esportivas de alto desempenho, o que antes se pensava não ser possível.

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Artigo 3

REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE III: RECOMENDAÇÕES PARA TREINAMENTO PÓS-TRANSPLANTE CARDÍACO

Juliana Beust de Lima,[1,2] Filipe Ferrari,[1,2] Ricardo Stein[1,2,3]

1. Grupo de Pesquisa em Cardiologia do Exercício do Hospital de Clínicas de Porto Alegre (CardioEx-HCPA)

2. Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares

3. Professor Adjunto do Serviço de Fisiatria e Reabilitação do Hospital de Clínicas de Porto Alegre da Universidade Federal do Rio Grande do Sul (HCPA-UFRGS)

Baseado nas diversas evidências expostas nesta revisão, o efeito benéfico do treinamento físico em indivíduos pós-transplante cardíaco (Txc) parece ser claro. Esta terapia se mostra segura e exequível, podendo ser realizada no ambiente hospitalar ou residencial. No entanto, embora ambas as estratégias sejam eficazes em promover aumento na capacidade funcional, de acordo com os experimentos realizados até o momento, a magnitude do efeito é maior quando o treinamento é realizado em ambientes controlados. É sugerido que no início do programa, após as devidas avaliações, os pacientes sejam continuamente monitorados por eletrocardiograma durante as sessões. No entanto, tal medida não é obrigatória, considerando que o benefício da terapia ultrapassa os potenciais riscos, que são de pequena magnitude. O corpo de evidências tem incluído, na sua maioria, pacientes com pelo menos seis meses após o procedimento. Entretanto, parecenos que quanto antes a intervenção for iniciada, maior o seu potencial benefício. De forma geral, diretrizes recomendam que o treinamento formal seja iniciado entre seis e oito semanas após o Txc. Essa recomendação visa à cicatrização do esterno, uma vez que a partir desse momento a maioria dos exercícios pode ser realizada. Cabe

salientar que os profissionais envolvidos com o processo de reabilitação desses pacientes devem avaliar quais são as atividades necessárias e seguras em cada etapa do processo.

A prescrição ideal inclui exercícios para promoção das diferentes valências físicas, sempre enfatizando o que é preconizado para cada condição. No cenário pós-Txc, o exercício aeróbico é a parte principal das sessões de treinamento, devendo ser complementado por exercícios resistidos e de flexibilidade dentro de um programa individualizado e periodizado. As sessões devem sempre iniciar com um período de aquecimento, assim como encerrarem com um desaquecimento controlado. Tal estratégia visa, além do aquecimento muscular e lubrificação das articulações, a um período para o ajuste da frequência cardíaca (FC) e pressão arterial (PA), ambas valências fisiológicas especialmente importantes nesta população tão particular.

O exercício aeróbico pode ser realizado em forma de caminhada ou ciclismo, tanto indoor, utilizando-se recursos como esteiras e/ou bicicletas ergométricas ou outdoor. Recomenda-se uma frequência semanal de três a cinco sessões, com duração de 20 a 40 minutos. Frequência e duração das sessões serão ajustadas conforme condições prévias do paciente e devem progredir ao longo do treinamento. O controle da intensidade é fundamental; devido ao maior número de evidências, preconiza-se o treinamento contínuo de moderada intensidade (TCMI) com consumo de oxigênio ($\dot{V}O_2$) entre o primeiro e segundo limiar ventilatório, com uma percepção de esforço referida entre 11 e 13 na Escala de Borg (quadro 1). O treinamento intervalado pode ser adotado, sendo uma estratégia para pacientes com maiores limitações, pelo fato deste poder ser realizado de forma intermitente em baixa e moderada intensidade, alternando blocos mais cansativos com períodos até mesmo de recuperação passiva. Ensaios clínicos randomizados demonstram que o treinamento intervalado de alta intensidade (TIAI) também pode ser um recurso útil e com maiores benefícios, mas até o momento se restringe aos pacientes com pelo menos seis meses de Txc. Os protocolos utilizados alternaram blocos de 30 segundos a quatro minutos em alta intensidade (80-100% do $\dot{V}O_2$ pico) com períodos de recuperação. Também é interessante considerar a associação de protocolos conforme as necessidades de cada indivíduo.

Os exercícios resistidos podem ser realizados com uma a três séries de 10 a 20 repetições para os principais grupos musculares, com uma frequência de duas a três sessões por semana. É recomendada a realização da avaliação da intensidade através da

Escala de Borg e esta deve ser referida entre 12 e 14 para adequada intensidade. No início do treinamento, exercícios sem carga externa, ou seja, apenas com peso corporal, podem ser considerados como estímulo suficiente para estes pacientes. Em seguida, bandas elásticas, halteres, caneleiras e aparelhos de musculação podem ser incluídos no programa de treinamento. Por fim, maior cuidado deve ser dado aos exercícios de membros superiores devido à toracotomia realizada.

Na Reabilitação Cardiovascular do Serviço de Fisiatria e Reabilitação do Hospital de Clínicas de Porto Alegre adotamos o seguinte protocolo na fase 2 da reabilitação: treinamento físico realizado em três sessões semanais, com tempo total de até 60 minutos; as sessões são compostas por exercício aeróbico em esteira e exercícios resistidos e de alongamentos/flexibilidade seguindo periodização preestabelecida (quadros 2 e 3), estruturada em macrociclo (36 sessões), mesociclos (12 sessões) e microciclos (seis sessões). Os ajustes na intensidade e duração dos exercícios são pré-estabelecidos, mas variáveis como velocidade e inclinação nos exercícios aeróbicos são ajustadas sistematicamente conforme a resposta cronotrópica, percepção de esforço e condição de cada paciente, visando sempre à manutenção da intensidade na zona alvo estipulada. Na primeira sessão, o exercício aeróbico pode ter duração de 10 a 25 minutos, de acordo com a capacidade do paciente, tendo como meta a realização de 30 minutos de exercício contínuo em moderada intensidade a partir da quinta semana. Na sétima semana, consideramos a alternância de sessões de TCMI com sessões de exercício intervalado, onde a intensidade pode ser maior. Qualquer exercício resistido só é iniciado a partir da sexta semana pós-Txc. A qualquer momento, se o paciente apresentar desconforto no tórax não são realizados exercícios para membros superiores e o paciente é encaminhado para avaliação médica. Exercícios de membros superiores são iniciados 90 dias após a cirurgia e evoluem de movimentos realizados em amplitudes articulares menores para maiores ao longo do treinamento, da mesma forma que as cargas, número de repetições e as séries, que são aumentadas progressivamente. Sendo assim, são realizadas de uma a três séries de exercício variando de 10 a 15 repetições. O tempo de recuperação é de aproximadamente um minuto entre cada série e os exercícios são ordenados de forma que se alternem os seguimentos exercitados (membros superiores e membros inferiores).

A FC, a PA e a percepção subjetiva de esforço avaliada pela escala de Borg são sempre controladas e registradas antes, durante e após as sessões de exercício. Segundo a Diretriz Sul-Americana de Prevenção e Reabilitação Cardiovascular,[1] pacientes com

PA sistólica e/ou diastólica acima de 190 mmHg e 120 mmHg, respectivamente, não são elegíveis para reabilitação até que a mesma esteja controlada. Alguns pesquisadores recomendam como ponto de corte uma PA sistólica de 160 mmHg e diastólica de 105mmHg. Para estes, caso os valores sejam superiores a sessão de exercício não deve ser iniciada.[2]

Considerações Finais

A reabilitação baseada em exercício é segura e pode promover diversos benefícios para pacientes pós-Txc. Assim, o exercício físico deve ser visto como parte integrante do manejo terapêutico para pessoas que receberam um novo coração. É importante que seja realizada uma minuciosa avaliação pré-participação para se verificar comorbidades após a cirurgia, como alterações hemodinâmicas e musculares, de modo a minimizar qualquer risco adverso durante e/ou após o treinamento. Evidências recentes demonstraram que o TIAI pode ser uma forma de treinamento viável para melhorar a capacidade funcional e a saúde global no cenário pós-Txc. Todavia, esse tipo específico de treinamento deve ser mais bem estudado nesses pacientes, antes de ser introduzido como prática rotineira. Além disso, estudos que comparem várias intensidades de exercício são desejáveis para que seja determinada alguma intensidade preferencial a ser adotada nos programas de reabilitação. Por fim, são necessárias pesquisas bem delineadas.

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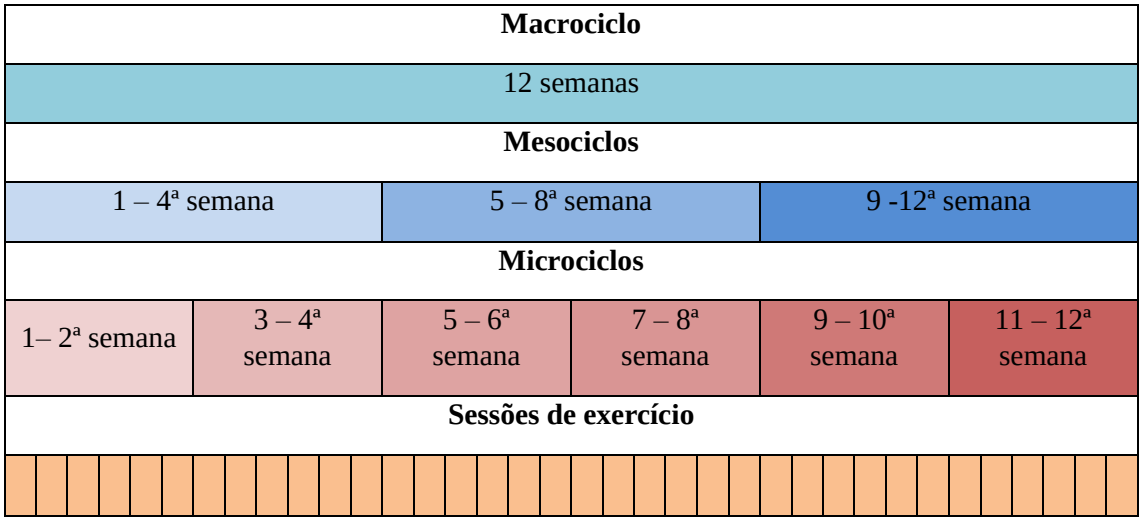
Figuras

Quadro 1. Intensidade do exercício

Zona alvo de intensidade	Limiares ventilatórios	% da FC máx.	Escala de BORG (6-20)
Moderada	1º-2º LV	60-70% da FC máx.	11-13
Alta	Acima do 2º LV	85-95% da FC máx.	15-17

LV: limiar ventilatório; FC: frequência cardíaca.

Quadro 2. Periodização do treinamento



Quadro 3. Protocolo de exercícios - CardioEx

Período do treinamento	Partes das sessões	Prescrição do exercício
Adaptação **1ª – 2ª semana**	**Exercício aeróbico**	10’ – 25’ intensidade moderada na esteira (aumento gradual na duração do exercício conforme condição do paciente)
	Exercícios resistidos	MI: Flexão de quadril (em pé) unilateral com caneleira - 0,5 – 1 kg Flexão de joelho (em pé) unilateral com caneleira - 0,5 – 1 kg Flexão plantar (em pé) - sem carga externa MS: Remada fechada com pegada neutra (em pé ou sentado) com elástico leve Supino fechado com pegada neutra (em pé ou sentado) com elástico leve • Para pacientes que relatarem desconforto no tórax não é necessário iniciar exercícios de MS nos primeiros treinos; Incluí-los conforme evolução do paciente; **Exercícios de MS devem ser iniciados após 90 dias da cirurgia.** **Qualquer exercício resistido só deverá ser realizado a partir da 6ª semana pós-Tx.** PSE: 3 – 5 na Escala de OMNI Exercícios alternados por seguimento 1 série de 10 – 15 repetições (aumento gradual nas repetições conforme evolução individual) Intervalo de 30 segundos a 1 minuto
	Alongamentos	Gastrocnêmio/sóleo plantar, quadríceps com auxílio e deltoide

Período do treinamento	Partes das sessões	Prescrição do exercício
Familiarização **3ª – 4ª semana**	**Exercício aeróbico**	**25’ intensidade moderada na esteira (aumento na velocidade conforme evolução do paciente)**
	Exercícios resistidos	MI: Flexão de quadril (em pé) unilateral com caneleira Flexão de joelho (em pé) unilateral com caneleira

		Flexão plantar (em pé) - sem carga externa MS: Remada fechada com pegada neutra (em pé ou sentado) com elástico leve Supino fechado com pegada neutra (em pé ou sentado) com elástico leve **Aumento na carga** das caneleiras e resistência do elástico conforme progressão e PSE individual PSE: 3 – 5 na Escala de OMNI Exercícios alternados por seguimento **2 séries de 15 repetições**
	Alongamentos	Gastrocnêmio/sóleo plantar, quadríceps e deltoide

Período do treinamento	**Partes das sessões**	**Prescrição do exercício**
5ª – 6ª semana	**Exercício aeróbico**	**30' intensidade moderada na esteira (aumento na velocidade conforme evolução do paciente)**
	Exercícios resistidos	MI: Flexão de quadril (em pé) unilateral com caneleira Flexão de joelho (em pé) unilateral com caneleira Flexão plantar (em pé) - sem carga externa MS: Remada fechada com pegada neutra (em pé ou sentado) com elástico leve Supino fechado com pegada neutra (em pé ou sentado) com elástico leve **Aumento na carga** das caneleiras e resistência do elástico conforme progressão e PSE individual PSE: 3 – 5 na Escala de OMNI Exercícios alternados por seguimento 2 séries de 15 repetições
	Alongamentos	**Cadeia posterior, quadríceps, deltoide, bíceps e peitoral, tríceps**

Período do treinamento	Partes das sessões	Prescrição do exercício
7ª – 8ª semana	**Exercício aeróbico**	**2 x na semana** 30’ moderada intensidade na esteira (**aumento na velocidade conforme evolução do paciente)** **1 x na semana: Intervalado na esteira utilizando aumento na velocidade (corrida) ou inclinação; 4 x 1’-2’ alta intensidade e 2’ moderada intensidade**
	Exercícios resistidos	MI: Flexão de quadril (em pé) unilateral com caneleira Flexão de joelho (em pé) unilateral com caneleira Flexão plantar (em pé) – **carga externa se necessário** MS: Remada fechada com pegada neutra (em pé ou sentado) com elástico Supino fechado com pegada neutra (em pé ou sentado) com elástico **Aumento na carga** das caneleiras e resistência do elástico conforme progressão e PSE individual PSE: 3 – 5 na Escala de OMNI Exercícios alternados por seguimento 2 séries de 15 repetições
	Alongamentos	Cadeia posterior, quadríceps, deltoide, bíceps e peitoral, tríceps

Período do treinamento	Partes das sessões	Prescrição do exercício
9ª – 10ª semana	**Exercício aeróbico**	**1 x na semana** 30’ moderada intensidade na esteira **(aumento na velocidade conforme evolução do paciente)** **2 x na semana:** Intervalado na esteira utilizando aumento na velocidade (corrida) ou inclinação; 4 x 1’-2’ alta intensidade e 2’ moderada intensidade
	Exercícios resistidos	MI: **Agachamento** – sem carga externa Flexão de joelho (em pé) unilateral com caneleira Flexão plantar (em pé) – carga se necessário

		MS: Remada fechada com pegada neutra (em pé ou sentado) com elástico **Supino (PI: ombros abduzidos) com pegada pronada** (em pé ou sentado) com elástico **Aumento na carga** das caneleiras e resistência do elástico conforme progressão e PSE individual PSE: 3 – 5 na Escala de OMNI Exercícios alternados por seguimento 2 séries de 15 repetições
	Alongamentos	Cadeia posterior, quadríceps, deltoide, bíceps e peitoral, tríceps

Período do treinamento	**Partes das sessões**	**Prescrição do exercício**
11ª – 12ª semana	**Exercício aeróbico**	1 x na semana 30’ moderada intensidade na esteira **(aumento na velocidade conforme evolução do paciente)** 2 x na semana: Intervalado na esteira utilizando aumento na velocidade (corrida) ou inclinação; 4 x **2’- 3’** alta intensidade e 2’ moderada intensidade
	Exercícios resistidos	MI 1.Agachamento – sem carga externa Flexão de joelho (em pé) unilateral com caneleira Flexão plantar (em pé) – carga se necessário MS: Remada fechada com pegada neutra (em pé ou sentado) com elástico Supino (PI: ombros abduzidos) com pegada pronada (em pé ou sentado) com elástico **Aumento na carga** das caneleiras e resistência do elástico conforme progressão e PSE individual PSE: 3 – 5 na Escala de OMNI Exercícios alternados por seguimento 2 séries de 15 repetições

	Alongamentos	Cadeia posterior, quadríceps, deltoide, bíceps e peitoral, tríceps

Período do treinamento	**Partes das sessões**	**Prescrição do exercício**
A partir de 3 meses	**Exercício aeróbico**	1 x na semana 30’ moderada intensidade na esteira **(aumento na velocidade conforme evolução do paciente)** e Intervalado na esteira utilizando aumento na velocidade (corrida) ou inclinação; **Possibilidades:** **4 x 2’ e 2’;** **4 x 3’ e 2’;** **4 x 4’ e 3’;**
	Exercícios resistidos	MI: Agachamento – sem carga externa Flexão de joelho (em pé) unilateral com caneleira Flexão plantar (em pé) – carga se necessário MS: Remada fechada com pegada neutra (em pé ou sentado) com elástico 2. Supino (PI: ombros abduzidos) com pegada pronada (em pé ou sentado) com elástico **Aumento na carga** das caneleiras e resistência do elástico conforme progressão e PSE individual PSE: 3 – 6 na Escala de OMNI Exercícios alternados por seguimento **2 - 3 séries** de 15 repetições
	Alongamentos	Cadeia posterior, quadríceps, deltoide, bíceps e peitoral, tríceps

MMII: membros inferiores; MMSS: membros superiores; PSE: percepção subjetiva do esforço.

- Exercício em esteira deve iniciar com 5’ de aquecimento e encerrar com 3’ de volta à calma em intensidades inferiores a parte principal
- Nunca atingir falha concêntrica nos exercícios resistidos

- A partir do 4º mês fadiga pode ser referida nas últimas 3 repetições nos exercícios resistidos
- Orientar respiração adequada durante os exercícios evitando a manobra de valsalva

Artigo 4

Exercise Training Modalities for Heart Transplant Recipients: A Systematic Review and Network Meta-Analysis Protocol

Authors and affiliations:

Juliana Beust de Lima, MSc[1,2,4], Douglas dos Santos Soares, MSc[1,4], Filipe Ferrari, MSc[1,2,4], Nelson Carvas Junior, MSc[5], Gabriel Carvalho[2], Santiago Alonso Tobar Leitão, MSc, PhD[1,4], Lívia Adams Goldraich, MSc[3,4], Nadine Clausell, MSc, PhD,[1,3,4,6] and Ricardo Stein, MSc, ScD[1,2,4,6]

[1] Graduate Program in Cardiology and Cardiovascular Sciences, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[2] Exercise Cardiology Research Group, Universidade Federal do Rio Grande do Sul, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[3] Heart Failure and Cardiac Transplant Unit, Cardiology Division, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[4] Interdisciplinary Research Group in Translational Cardiology, Clinical Research Center, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS - Brazil

[5] Department of Evidence-Based Health, Brazilian Cochrane Center, Universidade Federal de São Paulo, São Paulo, SP - Brazil

[6] Associate Professor, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS – Brazil

Corresponding author

Juliana Beust de Lima, MSc
Serviço de Fisiatria e Reabilitação, Hospital de Clínicas de Porto Alegre
Rua Ramiro Barcelos, 2350
Porto Alegre, RS 90035-903, Brazil
E-mail: julianabeustdelima@gmail.com

Word count: 2977

Authors' contributions

Conception of the study: JBL, DSS, FF, ST, RS
Major drafters of the protocol: JBL, DSS, FF, NCJ, RS
Minor drafters of the protocol: ST, GC
Provided feedback to the protocol: LAG, NC, RS
Data extraction and synthesis: FF, NCJ, JBL

Guarantor of the review

Juliana Beust de Lima, MSc

Statement

The protocol of this network meta-analysis was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement and the PRISMA-P 2015 Explanation and Elaboration Document.

Registration This systematic review and network meta-analysis was prospectively registered at the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020191192).

Amendments

This is the first version of the protocol. Any amendments to the protocol will be updated and published on the PROSPERO database.

Funding statement

This protocol was partially supported by the Hospital de Clínicas de Porto Alegre Research Incentive Fund (FIPE-HCPA), Porto Alegre, Brazil – Project number 2018-0292. JBL and GC are granted by the Conselho Nacional de Pesquisa e Desenvolvimento (CNPq). DSS and FF are granted by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES).

Role of the sponsor

This study is conducted by an academic institution and a research group that has no relationship with the pharmaceutical industry.

Competing interests

All authors declare that they have no competing interests.

Abbreviations

CPET: cardiopulmonary exercise test; ET: exercise training; HR: heart rate; HTx: heart transplant; OUES: oxygen uptake efficiency slope; peak VO_2: peak oxygen consumption; V_E/VCO_2 slope: minute ventilation relative to carbon dioxide production, an index of ventilatory efficiency; V_E: minute ventilation; VO_2/HR: oxygen pulse.

ABSTRACT

Introduction: Heart transplantation is the gold standard treatment for selected patients with end-stage heart failure. Although this procedure can improve quality and prolong life expectancy, several of these patients persist with decreased exercise tolerance. Evidence suggests that exercise training can bring multifactorial benefits to heart transplant (HTx) recipients. However, it is unclear which exercise modality should be preferred. Therefore, the aim of this systematic review and network meta-analysis is to compare the efficacy and safety of different training modalities in HTx recipients.

Methods and analysis: We will perform a comprehensive literature search in PubMed/MEDLINE, Embase, The Cochrane Library, CINAHL, Scopus, SportDISCUS, Web of Science Core Collection, and PEDro from inception until November 2020. Two registries (ClinicalTrials.gov and REBEC) will also be searched for potential results in unpublished studies. There will be no restriction on language, date of publication, publication status, or sample size. We will include randomized controlled trials enrolling adult HTx recipients with the presence of at least one exercise training group, which might be compared with another training modality and/or a non-exercise control group for a minimum of 4 weeks of intervention. The primary outcomes will be peak oxygen consumption and occurrence of adverse events. As secondary outcomes, the interaction between pulmonary ventilation, pulmonary perfusion, and cardiac output, oxygen uptake efficiency slope, heart rate response, oxygen pulse, peak blood pressure, and peak subjective perception of effort. In addition, we will evaluate the 6-minute walking distance, health-related quality of life, endothelial function, muscle strength, body fat percentage, and lean mass. Risk of bias will be assessed using the Cochrane RoB 2.0 tool, and we plan to use the Confidence in Network Meta-Analysis (CINeMA) tool to assess confidence in the results. All materials (raw data, processed data, statistical code and outputs) will be shared in a public repository.

Ethics and dissemination: Given the nature of this study, no ethical approval will be required. We believe that the findings of this study may show which is the most efficacious and safe physical training modality for HTx recipients. The completed systematic review and network meta-analysis will be submitted to a peer-reviewed journal.

PROSPERO registration number: CRD42020191192.

Keywords: heart transplantation, exercise training, cardiorespiratory fitness, heart rate, health-related quality of life, safety.

Strengths and limitations of this study

- This protocol was guided by PRISMA-P statement, registered in the PROSPERO database, and Open Science Framework platform.
- We will perform a comprehensive literature review with no restrictions on language, publication date, publication status, or sample size.
- The study will be guided by the Cochrane Handbook for Systematic Reviews of Interventions, version 6.1, in order to enhance the quality of the study.
- A potential limitation, inherent in the methodology of this study, is that indirect comparisons provide observational evidence across randomized trials and may suffer from the potential biases of observational studies, such as confounding bias.

INTRODUCTION

Heart transplantation (HTx) is the treatment of choice for selected patients with end-stage heart failure, representing the pinnacle of available therapy.[1] Although transplantation improves quality of life and increases life expectancy,[2,3] HTx recipients frequently experience impaired functional capacity,[4] in addition to other complications inherent to the use of immunosuppressants.[5] Reduced exercise tolerance, measured by peak oxygen consumption (peak VO_2), occurs secondary to damage to both the central (cardiac and pulmonary) and peripheral (vascular and skeletal muscle) components.[6]

In this sense, concomitantly with prevention of HTx-related complications and control of cardiac risk factors, a structured exercise-based rehabilitation program is recommended and may be an adequate strategy to assist in secondary prevention in these patients.[7-9] Evidence suggests a multifactorial beneficial effect of exercise training (ET) in HTx recipients.[6] Small randomized controlled trials have shown that rehabilitation improves autonomic control (both cardiac and peripheral),[10] muscle strength, and body composition,[11] while for endothelial function, synthesis of a small body of evidence shows high heterogeneity and the effect remains unclear.[12] Additionally, in a Cochrane systematic review and meta-analysis, ET was efficacious for increasing peak VO_2.[13] However, considering the broader spectrum of exercise interventions, it is unknown whether any modality is superior in terms of efficacy or potential for harm. In addition, synthesizing the effect of ET on other clinically relevant outcomes will assist in understanding the therapeutic potential of ET in secondary prevention in this population.

Different ET modalities have been studied in patients after HTx, such as endurance training (moderate-intensity continuous and high-intensity interval training),[13-15] resistance training,[11,16] and the combination of both.[17,18] Indeed, combined ET is the most recommended modality for cardiovascular rehabilitation, despite the lack of robust

evidence of its superiority over other modalities in this specific population.[8,9] In addition, there is little information about the characteristics of ET (e.g., frequency, intensity, volume and type), as well as differences in adaptation depending on whether training is begun early or late after surgery. Even less is known about the true effect of ET on other relevant parameters beyond peak VO_2 in the HTx scenario.

In patients with heart failure, some variables measured by cardiopulmonary exercise testing (CPET), such as peak VO_2, the ratio of minute ventilation (VE) to carbon dioxide production (VE/VCO_2 slope),[19,20] and heart rate (HR) recovery after ET[21] were identified as important prognostic markers. However, in HTx, the evidence base is much less clear. In a retrospective study, peak VO_2 and self-reported functional capacity were found to be strong predictors of survival in HTx recipients.[22] In turn, muscle strength and body fat seem to influence exercise capacity.[23] Interestingly, while the main limiting symptom for ET before HTx was dyspnea, after the procedure, patients reported interruption of exercise due to leg fatigue and muscle exhaustion.[4] In addition, another important factor is the chronotropic response to ET[24] due to the involvement of a denervated heart in increasing HR, contributing to the reduction of exercise tolerance and influencing adaptations to ET.[25,26]

In this systematic review and network meta-analysis, we will compare the safety and efficacy of different modalities of ET based on peak VO_2 improvement. Furthermore, we will quantify the effect of ET on important outcomes that have not yet been scrutinized, while exploring factors that may influence physiological adaptations to ET.

Objectives

Primary objectives

- To compare the efficacy of different ET modalities (moderate-intensity continuous training, high-intensity interval training, resistance training, and combined aerobic plus resistance training considering both center-based and home-based ET) in improving peak VO_2 in HTx recipients;
- To compare rates of adverse events, such as vertigo, dizziness, musculoskeletal complaints, syncope, hypotension, elevated blood pressure, or cardiovascular events (angina, arrhythmias, myocardial infarction, stroke and death) during and after sessions of different ET modalities.

Secondary objectives

- To compare quantitatively, through meta-analysis (ET *versus* usual care) and, if possible, through network meta-analysis, the efficacy of moderate-intensity continuous training, high-intensity interval training, resistance training, and combined training (center-based and home-based ET) in regard to the following variables: VE/VCO_2 slope, oxygen uptake efficiency slope (OUES), HR (rest, peak and recovery), peak oxygen pulse (VO_2/HR), peak systolic and diastolic blood pressure, Borg Rating of Perceived Exertion scale, 6-minute walk test distance, health-related quality of life, endothelial function, muscle strength, and fat and lean mass percentage;

- To compare quantitatively, through meta-analysis (ET *versus* usual care), the efficacy and safety of ET in the following subgroups: patients after recent (<6

months) *versus* late HTx and those receiving center-based *versus* home-based ET, as well as at different follow-up periods.

METHODS

This protocol was guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement[27] (see checklist in **Supplementary Material 1**) and the PRISMA-P 2015 Explanation and Elaboration Document.[28] The same documents, as well as the PRISMA Extension for Network Meta-Analysis of Health Care Interventions,[29] will be used to prepare the final report. In addition, the study will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions version 6.1.[30] This systematic review and network meta-analysis was registered in the International Prospective Register of Systematic Reviews – PROSPERO (CRD42020191192). All study materials will be shared publicly through the Open Science Framework tool, available at: https://osf.io/3rwxb/.

Eligibility criteria

This systematic review will be based on Population, Intervention, Comparator, Outcome, and Setting (PICOS) criteria.

Participants

(a) HTx recipients aged ≥18 years, regardless of sex and race; (b) Patients receiving immunosuppressive therapy according to the transplant center protocol, who did not experience severe complications or high-grade rejection on cardiac biopsies during the ET period. Studies enrolling heterotopic transplant recipients or multiorgan transplant recipients will be excluded.

Interventions

We will consider ET as a single strategy or as a component of a comprehensive cardiac rehabilitation program (after hospital discharge), considering a minimum intervention period of 4 weeks. Center-based and home-based interventions will also be considered for the following modalities: moderate-intensity continuous training, high-intensity interval training, resistance training, and combined training (aerobic plus resistance).

Comparators

For network meta-analysis, by the very nature of this study, we will compare the eligible interventions among themselves. For the parallel meta-analysis, we will compare the interventions with their respective control groups (non-ET or usual care).

Outcomes

Primary outcomes

Peak VO_2 measured through CPET in $L.min^{-1}$ and $mL.kg^{-1}min^{-1}$, whenever available. Rate of adverse events through the absolute and relative frequency of occurrences described in the safety outcomes.

Secondary outcomes

Other CPET variables: VO_2/HR in mL/beat and both slopes, VE/VCO_2 slope and OUES as absolute measures. HR (rest, peak, and recovery) in beats/min, peak systolic and diastolic blood pressure in mmHg, and Borg Rating of Perceived Exertion score. Other secondary outcomes: 6-minute walk distance (in meters), health-related quality of

life using validated instruments (e.g., the 36-Item Short-Form Health Survey and World Health Organization Quality of Life questionnaire), and endothelial function by absolute (mm) and relative (%) flow-mediated dilation. Upper and lower extremity maximal strength in kilograms assessed using one-repetition maximum (1RM) testing or another equivalent method (e.g., isokinetic evaluation [Nm], sit-to-stand movements in 1 min and hand grip strength test). Relative (%) and absolute (kg) fat mass and lean mass, preferably measured through dual-energy X-ray absorptiometry or bioelectrical impedance analysis.

Safety outcomes

Whenever data is available in the randomized controlled trial, we will quantitatively analyze the occurrence of adverse events – such as vertigo, dizziness, musculoskeletal complaints, syncope, hypotension, elevated blood pressure, or cardiovascular events (angina, arrhythmias, myocardial infarction, stroke, and death) – during and after exercise sessions.

Study designs

Only randomized controlled trials (parallel-group, crossover, or cluster design) will be included. Crossover trials will be considered in their full form only if there is a washout period of at least 4 weeks. No restrictions will be imposed on language or date of publication.

Information sources and search

Electronic search strategies

For a comprehensive survey of the literature, the following databases from inception to November 2020 will be searched: PubMed/MEDLINE, Cochrane Library,

Embase, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), Scopus, SportDISCUS, Web of Science Core Collection, and Physiotherapy Evidence Database (PEDro). Two registries (ClinicalTrials.gov and REBEC) will also be searched for potential results in unpublished studies. We will also review the gray literature, which includes repositories of dissertations and theses, conference publications, and preprint repositories and databases. Authors will be contacted if further data are required. A hand search of the reference lists of included studies will be also conducted.

Search strategy

The main electronic search strategy was designed for PubMed/MEDLINE and will be adapted as appropriate for each of the other databases. Queries will be developed using MeSH terms and their synonyms, and Boolean operators (where possible) to improve searches. Keywords and MeSH terms include: "heart transplantation", "exercise", "resistance training", "physical endurance", and "circuit-based exercise". Comprehensive search strategies for all the databases that will be consulted are included in the **Supplementary Material 2**.

Study records

Data managements and selection process

Data extraction will be based on the following steps: (1) In Clarivate Analytics Endnote X9® (2018) reference management software, the reviewer (FF) will set up a library to gather all studies retrieved from the aforementioned databases; (2) all duplicates will be excluded; (3) the titles and abstracts will be evaluated by two independent reviewers (FF and JBL) for classification as potentially eligible or non-eligible. Divergences will be solved by consensus between reviewers, and, if necessary, a third

opinion (RS) will be requested; (4) studies classified as potentially eligible will be read in full, and discrepancies will be solved by the same previous method; (5) the studies excluded in the previous stage will be compiled in an Excel worksheet, followed by their respective reasons for exclusion (no design of interest, no population of interest, no intervention of interest, no endpoints of interest, or other). The results of the selection process will be presented in a flow diagram, as shown in the **Supplementary Material 3.**

Data collection process and data items

Data will be extracted by two independent reviewers (FF and JBL). Disagreements will be solved by consensus, and, if necessary, a third opinion (RS) will be requested. The reviewers will not be blinded to the authors' names, institutions, or periodicals. The following information will be extracted:

- Study characteristic: first author, journal's name, year of publication, conflict of interest, publication type, study design (parallel, crossover, or cluster randomized controlled trial), washout period (weeks), study period (weeks), country, language of the publication, and number of patients randomized;
- Patient baseline characteristics: age, weight, height, body mass index, sex, time since transplantation, immunosuppressant therapy, comorbidities, etiology and duration of heart failure, surgical technique, previous exercise-based rehabilitation (phase 1), and presence of possible additional interventions to training; in addition, outcome assessment methods; equipment used (cycle ergometer or treadmill) and peak respiratory exchange ratio (peak R), when CPET performed;

- Interventions and comparators: training modality, material resources, intended target zone and form of intensity control, session volume, weekly frequency and follow-up period; supervisory level information, if center-based or home-based ET.
- Results: number of participants in each group, pre and post-intervention values, deltas, standard deviations, or other measures of dispersion, and P-values.

Geometry of the network

The forest.netmeta function of the netmeta package will be used to build and present the geometry of different interventions. In the graph, nodes will be used to represent the intervention and edges to show comparisons between interventions. Besides qualitative descriptions and graphs, we will provide quantitative metrics assessing features of network geometry, such as diversity, co-occurrence, and homophily.

Risk of bias within individual studies

The risk of bias will be assessed using the Cochrane RoB 2.0 tool.[31] The assessment of the studies will be performed independently by two reviewers (DSS and ST); any disagreements will be resolved by consensus or by discussion with a third researcher (JBL). Evaluation of quality will be divided into five items: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; (5) bias in selection of the reported result. Also, the risk of bias will be classified into three categories: (1) Low risk of bias; (2) Some concerns; and (3) High risk of bias.

Publication bias

To investigate the influence of small-study effects, we will use the visual inspection method of funnel plot if at least ten studies are included in a meta-analysis, followed by Egger's test.[32]

Data synthesis

Main analyses

We will use difference in means as the principal summary measure of the effect to express comparisons between interventions, associated with the 95% confidence interval (95% CI) as a measure of uncertainty. When the same outcome is presented by different measures, the standardized mean difference will be applied. As a summary measure of dichotomous variables, we will use the risk ratio (RR). If quantitative synthesis is not appropriate, a systematic narrative synthesis will be provided.

For continuous variables, we will extract the mean (or other measure of central tendency) and standard deviation (or other measure of dispersion) of variables at baseline and in the follow-up in each arm of the studies. When available, we plan to obtain the mean change from baseline and standard deviation or other measures of dispersion in each arm of the trials. For dichotomous outcomes, we will collect absolute and relative frequencies in each treatment arm.

Planned methods of analysis

We plan to use the netmeta package version 1.2-1 implemented in R-3.6.2 software for Mac to perform a network meta-analysis[33] and synthesize direct and indirect evidence of the therapeutic effects of the interventions. Node-splitting method will be used to assess inconsistencies between direct and indirect comparisons when observing a

loop connecting three arms. We will present a treatment ranking by P-scores based on the point estimates and standard error of the available network.

Additional analyses

We plan to perform analyses to compare quantitatively, through meta-analysis (ET *versus* usual care), the efficacy and safety of ET in two subgroups: patients after recent (less than 6 months) *versus* late HTx and center-based *versus* and home-based ET, as well as different follow-up periods. In case of significant heterogeneity or inconsistency, a subgroup analysis will be performed to explore, when possible, the following variables: age, sex, and comorbidities. Finally, a sensitivity analysis will be performed for the inclusion of studies with high risk of bias and/or missing data.

Risk of bias across studies

We plan to use the CINeMA (Confidence in Network Meta-Analysis) tool[34,35] to assess confidence in the results. CINeMA considers six domains – within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence – and assigns judgments at three levels (no concerns, some concerns, or major concerns). For each treatment effect, adjudicate levels of confidence corresponding to the usual Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) assessments of very low, low, moderate, or high will be utilized.

Patient and public involvement

No patient involved.

ETHICS AND DISSEMINATION

Given the nature of this study, no ethical approval will be required. The completed systematic review and network meta-analysis will be submitted to a peer-reviewed journal.

Authors Information

Juliana Beust de Lima: orcid.org/0000-0002-5408-2457

Douglas dos Santos Soares: orcid.org/0000-0002-9166-7614

Filipe Ferrari: orcid.org/0000-0001-6929-8392

Nelson Carvas Junior: orcid.org/0000-0003-2168-8927

Gabriel Carvalho: orcid.org/0000-0001-7792-826X

Santiago Alonso Tobar Leitão: orcid.org/0000-0002-4163-7783

Livia Adams Goldriach: orcid.org/0000-0002-1523-4286

Nadine Clausell: orcid.org/0000-0003-4207-3809

Ricardo Stein: orcid.org/0000-0003-2357-5176

Acknowledgements

The authors of this protocol thank Bárbara Pilatti Piffer, staff librarian at Universidade Federal do Rio Grande do Sul, for her contributions in design of the search strategies and retrieval of documents.

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Supplementary material 1. PRISMA-P 2015 CHECKLIST.

Section/topic	#	Checklist item	Information reported		Page
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	2, 5 and 9
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	2
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	2
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	2
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	6-7
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	8-9
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	9-11
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey	☒	☐	11-12

Section/topic	#	Checklist item	Information reported		Page
			Yes	No	
		literature sources) with planned dates of coverage			
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	12
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	12-13
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	12-13
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	13
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	13-14
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	10-11
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	14
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	15-16
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	15-16
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	15

Section/topic	#	Checklist item	Information reported		Page
			Yes	No	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	14-16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	16

According to the document sent for review.

Supplementary material 2. Bibliographic databases and search strategies.

PubMed/MEDLINE
(((heart transplantation[MeSH] OR heart transplant*[tw] OR cardiac transplant*[tw] OR heart recipient*[tw] OR heart transplant*[tw] OR new heart[tw] OR heart grafting[tw] OR cardiac grafting[tw] OR cardiac allograft*[tw] OR cardiac graft*[tw] OR heart graft*[tw])) AND ((exercise[MeSH] OR exercise*[tw] OR physical training[tw] OR physical exercise*[tw] OR high-intensity interval training*[tw] OR high intensity interval training*[tw] OR high-intensity intermittent exercise*[tw] OR high-intensity exercise*[tw] OR sprint interval training*[tw] OR resistance training[MeSH] OR strength training[tw] OR aerobic exercise*[tw] OR aerobic training*[tw] OR physical endurance[MeSH] OR resistance exercise*[tw] OR exercise therapy[MeSH] OR exercise therap*[tw] OR combined training[tw] OR concurrent training[tw] OR concurrent exercise*[tw] OR circuit-based exercise[MeSH] OR circuit based exercise*[tw] OR circuit training[tw] OR combined training[tw] OR combined exercise*[tw] OR exercise-based rehabilitation[tw] OR training based rehabilitation[tw] OR isometric exercise*[tw] OR home-based exercise*[tw] OR home-based training[tw] OR rehabilitation exercise*[tw] OR weight training[tw] OR weight exercise*[tw] OR weight lifting*[tw] OR weightlifting exercise[tw] OR weightlifting exercises[tw]))) AND (("randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "clinical trial"[pt] OR "random allocation"[mh] OR "double-blind method"[mh] OR "clinical trial"[pt] OR ("clinical trial"[tw]) OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw])) OR ("latin square"[tw]) OR placebos[mh] OR placebo*[tw] OR random*[tw] OR research design[mh:noexp] OR follow-up studies[mh] OR prospective studies[mh] OR cross-over studies[mh] OR control*[tw] OR prospectiv*[tw] OR volunteer*[tw]))
Cochrane
#1 MeSH descriptor: [Heart Transplantation] explode all trees
#2 "heart transplantation*" OR "cardiac transplant*" OR "heart recipient*" OR "heart transplant*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*"
#3 #1 or #2
#4 MeSH descriptor: [Exercise] explode all trees
#5 MeSH descriptor: [Exercise Therapy] explode all trees
#6 MeSH descriptor: [Physical Fitness] explode all trees
#7 MeSH descriptor: [High-Intensity Interval Training] explode all trees
#8 MeSH descriptor: [Resistance Training] explode all trees
#9 MeSH descriptor: [Physical Endurance] explode all trees
#10 MeSH descriptor: [Circuit-Based Exercise] explode all trees
#11 exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity

intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*"

#12 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11

#13 #3 and #12 in Trials

Scopus

#1 TITLE-ABS-KEY("heart transplantation*" OR "cardiac transplant*" OR "heart recipient*" OR "heart transplant*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*")

#2 TITLE-ABS-KEY(exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*")

#3 (INDEXTERMS ("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials" OR "random allocation" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "multicenter study" OR "double blind procedure" OR "single blind procedure" OR "crossover procedure" OR "clinical trial" OR "controlled study" OR "randomization" OR "placebo")) OR (TITLE-ABS-KEY (("clinical trials" OR "clinical trials as a topic" OR "randomized controlled trial" OR "Randomized Controlled Trials as Topic" OR "controlled clinical trial" OR "Controlled Clinical Trials as Topic" OR "random allocation" OR "randomly allocated" OR "allocated randomly" OR "Double-Blind Method" OR "Single-Blind Method" OR "Cross-Over Studies" OR "Placebos" OR "cross-over trial" OR "single blind" OR "double blind" OR "factorial design" OR "factorial trial"))) OR (TITLE-ABS (clinical trial* OR trial* OR rct* OR random* OR blind*))

SPORTDiscus

(DE "HEART transplantation" OR "heart transplant*" OR "cardiac transplant*" OR "heart recipient*" OR "cardiac allograft") AND (DE "EXERCISE" OR DE "RESISTANCE training" OR DE "PHYSICAL fitness" OR DE "EXERCISE therapy" OR "physical training" OR "physical exercise*" OR "high-intensity interval training*"

OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*")

CINAHL

(MH "heart transplantation" OR OR "heart transplantation*" OR "cardiac transplant*" OR "heart recipient*" OR "heart transplant*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*") AND (MH "Exercise" OR MH "Resistance Training" OR MH "Therapeutic Exercise" OR OR exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*")

Web of Science

ALL=("heart transplant*" OR "cardiac transplant*" OR "heart recipient*" OR "new heart" OR "cardiac graft*" OR "cardiac allograft recipients" OR "heart graft*") AND ALL=(exercise* OR "physical training" OR "physical exercise*" OR "high-intensity interval training*" OR "high intensity interval training*" OR "high-intensity intermittent exercise*" OR "high-intensity exercise*" OR "sprint interval training*" OR "strength training" OR "aerobic exercise*" OR "Aerobic training" OR "resistance exercise*" OR "exercise therap*" OR "combined training" OR "concurrent training" OR "concurrent exercise*" OR "circuit based exercise*" OR "circuit training" OR "combined training" OR "combined exercise*" OR "exercise-based rehabilitation" OR "training based rehabilitation" OR "isometric exercise*" OR "home-based exercise*" OR "home-based training" OR "rehabilitation exercise*" OR "weight training" OR "weight exercise*" OR "weight lifting*" OR "weightlifting exercise*") AND (TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*))

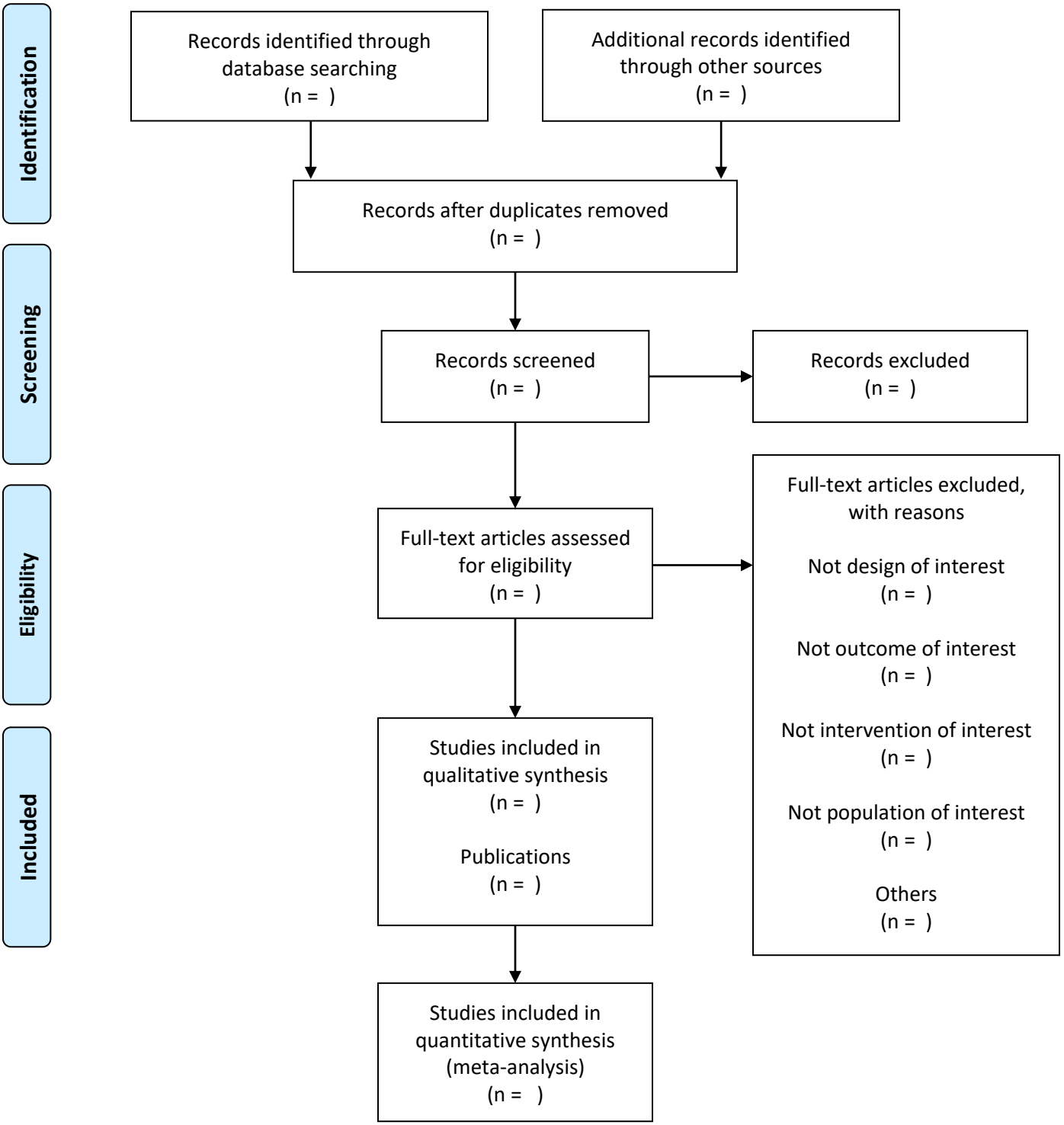
Embase

('heart transplantation'/exp OR 'cardiac transplantation' OR 'heart allograft' OR 'heart allotransplantation' OR 'heart heterograft' OR 'heart heterotransplantation' OR 'heart homograft' OR 'heart homotransplantation' OR 'heart orthotopic transplantation' OR

'heart tissue transplantation' OR 'heart transplantation' OR 'heart ventricle transplantation' OR 'human heart transplantation' OR 'transplantation, heart' OR 'heart graft'/exp OR 'cardiac graft' OR 'cardiac transplant' OR 'heart graft' OR 'heart graft survival' OR 'heart transplant' OR 'transplant, heart') AND ('aerobic exercise'/exp OR 'aerobic dance' OR 'aerobic dancing' OR 'aerobic exercise' OR 'aerobics' OR 'aerobics exercise' OR 'dancing, aerobic' OR 'exercise, aerobic' OR 'low impact aerobic exercise' OR 'low impact aerobics' OR 'step aerobics' OR 'exercise'/exp OR 'biometric exercise' OR 'effort' OR 'exercise' OR 'exercise capacity' OR 'exercise performance' OR 'exercise training' OR 'exertion' OR 'fitness training' OR 'physical conditioning, human' OR 'physical effort' OR 'physical exercise' OR 'physical exertion' OR 'restraint, physical' OR 'resistance training'/exp OR 'resistance exercise' OR 'resistance exercise training' OR 'resistance training' OR 'strength training' OR 'weight bearing exercise' OR 'kinesiotherapy'/exp OR 'sktm (specialized kinesitherapeutic methodology)' OR 'corrective exercise' OR 'exercise movement techniques' OR 'exercise therapy' OR 'exercise treatment' OR 'kinesiotherapeutic intervention' OR 'kinesiotherapeutic method' OR 'kinesiotherapeutic procedure' OR 'kinesiotherapeutic technique' OR 'kinesiotherapeutical treatment' OR 'kinesiotherapy' OR 'kinesitherapeutic exercises' OR 'kinesitherapeutic intervention' OR 'kinesitherapeutic method' OR 'kinesitherapeutic methodology' OR 'kinesitherapeutic procedure' OR 'kinesitherapeutic technique' OR 'kinesitherapeutic treatment' OR 'kinesitherapeutical treatment' OR 'kinesitherapy' OR 'specialised kinesitherapeutic methodology' OR 'specialized kinesitherapeutic methodology' OR 'therapeutic exercise' OR 'therapy, exercise' OR 'treatment, exercise') AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomi?ed controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*)
Pedro
“Heart transplant”
ClinicalTrials.gov – grey literature
Condition or disease: heart transplant Study type: interventional studies (clinical trials) Study results: all studies Status: active, not recruiting, terminated, completed, unknown status Age group: adult and older adult Sex: all Intervention/treatment: exercise
REBEC – grey literature

Trials containing the terms: “heart transplant” and exercise Study type: Interventional Inclusion gender: both Recruitment situation: recruitment completed, premature termination and complete data analysis Minimum age for inclusion: 18 years
OpenGrey – grey literature
“heart transplant” and exercise
Google Scholar – grey literature
“heart transplant” and exercise We will review the first 300 search results.

Supplementary material 3. PRISMA 2009 FLOW DIAGRAM.



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit www.prisma-statement.org.