Universidade Federal do Rio Grande do Sul

Programa de Pós-Graduação em Ciências da Saúde:

Cardiologia e Ciências Cardiovasculares

Associação das variáveis de prescrição de exercício e características clínicas com efeitos do treinamento aeróbico em pacientes com insuficiência cardíaca com fração de ejeção reduzida: revisão sistemática e meta-análise

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Orientador: Dr. Daniel Umpierre de Moraes

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Tese de doutorado apresentada como requisito parcial para obtenção de título de Doutora em Ciências Cardiovasculares, à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Ciências da Saúde: Ciências Cardiovasculares.

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“Nós, para os outros, apenas criamos pontos de partida.”

Simone de Beauvoir

SUMÁRIO

LISTA DE ABREVIATURAS

bpm: batimentos por minuto

ECRs: ensaios clínicos randomizados

EF: *ejection fraction*

FC: frequência cardíaca

FE: fração de ejeção

HF: *heart failure*

HR: *heart rate*

HFrEF: *heart failure with reduced ejection fraction*

IC: insuficiência cardíaca

IC 95%: Intervalo com 95% de confiança

LV_1: primeiro limiar ventilatório

RAR: redução absoluta do risco

RC: razão de chances

RCT: *randomised controlled trial*

RR: risco relativo

RS: revisão sistemática

MA: meta-análise

NYHA: *New York Heart Association*

SRMA: systematic review and meta-analysis

TCPE: teste cardiopulmonar de exercício máximo

VO_2: consumo de oxigênio

V_E/VCO_2: ventilação minuto / produção de dióxido de carbono

VT: *ventilatory threshold*

WMD: *weighted mean difference*

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CAPÍTULO I

1. Introdução

A insuficiência cardíaca (IC) é uma síndrome caracterizada por sintomas típicos (fadiga, dispneia), que podem estar acompanhados de sinais (ausculta pulmonar com crepitações, turgência jugular, edema periférico). Um dos principais sintomas na IC é a intolerância ao exercício. Devido a isso, a reabilitação cardíaca com ênfase no exercício está entre os tratamentos recomendados para os pacientes[1-3].

Revisões sistemáticas (RS) com meta-análise (MA) têm demonstrado os benefícios do exercício para pacientes com IC na melhora do consumo de oxigênio (VO_2), fração de ejeção (FE) do ventrículo esquerdo, qualidade de vida, entre outros. Entretanto, o perfil dos pacientes (sexo, idade, New York Heart Association - NYHA, uso de beta-bloqueadores) e as características dos programas de treinamento (modalidade de teste/treino, intensidade, volume de treino, supervisão) variam consideravelmente entre os ensaios clínicos randomizados (ECRs) incluídos nas revisões[4-17].

O sexo feminino vem sendo pouco representado nos estudos sobre exercício e IC, sendo, inclusive, um critério de exclusão em 36% dos estudos[14,16]. Por outro lado, análises que levaram o sexo em consideração indicaram que as pacientes poderiam se beneficiar mais do treinamento do que homens, por apresentarem valores mais baixos de VO_2 pico[4,18,19]. Outra característica que apresenta diferenças entre os estudos é o percentual de pacientes em uso de beta-bloqueadores. Lembrando que o uso deste medicamento apresenta associação com a redução da morbidade e mortalidade nos pacientes[20].

Investigações sobre os efeitos da combinação do volume e intensidade de treinamento com exercício aeróbico demonstraram que somente pacientes que atingem uma carga mínima de treinamento semanal apresentam redução de eventos clínicos (mortalidade e hospitalizações)[21]. Quando observado exclusivamente o efeito da intensidade, alvos mais altos de treinamento também parecem trazer maiores benefícios para os pacientes[22,23]. Além disto, cabe ressaltar que uma mesma intensidade relativa utilizada para a prescrição do exercício aeróbico, quando aplicada em diferentes ergômetros, pode produzir respostas diferentes nos pacientes[24]. Um mesmo sujeito pode atingir valores de VO_2 pico, primeiro limiar ventilatório (LV_1), FC máxima e, consequentemente, menor débito cardíaco quando avaliado em cicloergômetro, em comparação com a esteira[25-32].

Tendo em vista que as características dos protocolos de treinamento e do perfil dos pacientes podem estar associadas a alterações nos efeitos do treinamento com exercício aeróbico na IC, desenvolvemos o presente estudo. O objetivo deste trabalho foi verificar os efeitos de diferentes protocolos de exercício e das características dos pacientes no VO_2 pico, ventilação minuto / produção de dióxido de carbono (V_E/VCO_2), FC máxima, LV_1, mortalidade e hospitalizações em pacientes com IC e FE reduzida submetidos ao treinamento aeróbico.

CAPÍTULO II

2. Revisão da literatura

2.1. Insuficiência cardíaca

O diagnóstico de IC se baseia na avaliação clínica, incluindo sinais e sintomas, associada com a avaliação da FE do paciente para determinar o tipo e a gravidade da doença. Pacientes com IC podem ser classificados em duas categorias pacientes com redução da FE e pacientes com FE preservada[1,3]. Os pacientes com IC e FE preservada apresentam taxas de mortalidade em torno de 32%, enquanto que o paciente com IC e FE reduzida a taxa é de 41% (segmento médio de 47 meses). Uma RSMA apresentou um risco relativo de 0,79 em benefício dos pacientes com IC com FE preservada, em comparação a IC com FE reduzida, acompanhados por uma média de 47 meses[33].

Em torno de 47% dos pacientes diagnosticados com IC apresentam FE preservada[34]. Porém, ainda há controvérsia sobre qual a FE que deve ser adotada como ponto de corte para determinar se a FE está reduzida, utilizando-se pontos de corte entre 35 e 50%[1,3]. A Diretriz Brasileira de IC utiliza um ponto de corte menor ou igual a 50% para diferenciar ambas [35].

Os pacientes com IC frequentemente apresentam redução da tolerância ao exercício devido à fadiga muscular, sendo a dispneia um dos sintomas mais frequentes da IC durante a realização de atividades físicas e sessões de exercício[1-3,35,36]. A dispneia ainda pode ser utilizada para indicar a severidade da doença por meio da classificação da NYHA, sendo também um sintoma muito comum para monitorar a resposta aos tratamentos. As classes da NYHA estratificam o grau de limitação funcional do paciente, variando de ausência dos sintomas em atividades cotidianas (classe I) a sintomas em repouso (classe IV)[1,3,35].

A redução da aptidão física se dá por fatores que envolvem mecanismos diretos da fisiopatologia da IC, tais como redução do débito cardíaco, alterações do controle pressórico e disfunção endotelial. Assim como, mecanismos associados com a miopatia, entre eles, alterações dos tipos de fibras musculares, redução da capacidade muscular oxidativa, alterações na matriz celular, na microcirculação e no manejo de cálcio, aumento da atrofia e apoptose muscular, e aumento das citocinas pró-inflamatórias. Tais prejuízos parecem estar relacionados ao descondicionamento dos pacientes[4,37-45].

A combinação destes fatores acarreta aumento da fadiga, redução do VO_2 pico e aumento do V_E/VCO_2 nos pacientes com IC[36,37,46]. Reduzindo, assim, suas atividades de vida diária e qualidade de vida relacionada a saúde, aumentando a frequência de reinternações e mortalidade[47]. Assim, um melhor entendimento sobre o que está associado com a fadiga muscular destes pacientes poderá auxiliar no tratamento destes pacientes[36].

O tratamento farmacológico da IC tem como eixo central o uso dos beta-bloqueadores, devido à melhora na classe funcional, redução da progressão dos sintomas e das hospitalizações[48-53]. Assim como, a associação dos inibidores da enzima conversora da angiotensina ou bloqueadores do receptor da aldosterona também aumentou a sobrevida dos pacientes[49,51,52]. O uso dos beta-bloqueadores adicionou benefícios quanto à melhora da aptidão cardiorrespiratória, obtida por meio do exercício prescrito aos pacientes, sem diferenças entre as categorias do medicamento (cardiosseletivos e não seletivos)[9].

O tratamento não farmacológico da IC envolve orientações relacionadas ao estilo de vida, o que inclui mudanças tanto da alimentação, quanto do nível de atividade física dos pacientes. Um dos principais objetivos do tratamento da IC é aumentar a capacidade de esforço físico dos pacientes[54]. As diretrizes da área que cobrem informações sobre etiologia, prevenção, diagnóstico e intervenções terapêuticas, indicam a reabilitação cardíaca com ênfase em exercício como uma intervenção segura e efetiva a ser indicada para os pacientes com IC (classe de recomendação I, nível de evidência A) [1,2,35,47,55,56].

2.2. Fatores prognóstico na IC e relacionados ao exercício

Existe um grande esforço da literatura para encontrar marcadores de prognóstico na IC, com o objetivo de otimizar a estratificação de risco dos pacientes. O teste cardiopulmonar de exercício máximo (TCPE) tem sido utilizado para avaliar a resposta do paciente ao esforço progressivo, devido ao poder prognóstico que as variáveis do TCPE podem apresentar no acompanhamento dos pacientes com IC[37,57].

Os primeiros estudos sobre os marcadores para estratificação do risco de mortalidade e hospitalização focaram no VO_2 pico. Com base no princípio de Fick, o VO_2 pico é determinado pelo produto do débito cardíaco e da diferença artério-venosa de oxigênio, e reflete o grau de prejuízo da função ventricular (bombeamento cardíaco), função vascular (entrega de oxigênio) e capacidade metabólica do musculo esquelético (utilização do oxigênio)[4,37].

Um estudo clássico de Mancini e colaboradores[58] demonstrou o potencial do VO_2 pico como marcador prognóstico dos pacientes com IC candidatos a transplante cardíaco. Os pacientes que apresentavam VO_2 pico menor ou igual a 14 $ml.kg^{-1}.min^{-1}$ tinham uma taxa de sobrevida em um ano de apenas 47%, enquanto que os demais pacientes apresentavam uma taxa de 94%. Devido a isso, adotou-se o ponto de corte de 14 $ml.kg^{-1}.min^{-1}$ para auxiliar na tomada de decisão da indicação de transplante cardíaco e esse critério é utilizado até os dias de hoje para escolha dos pacientes que irão receber formalmente a indicação de transplante.

Existe uma associação entre a severidade da IC e a ventilação excessiva, o que justifica o estudo da eficiência ventilatória nestes pacientes. Uma das maneiras de verificar a eficiência ventilatória é por meio da relação V_E/VCO_2, a qual simplificadamente reflete o aproveitamento ventilatório para a eliminação de CO_2. Dessa forma, quanto mais baixos os valores de V_E/VCO_2, melhor é a resposta do paciente ao exercício[37]. Em 1997, MacGowan e colaboradores[59] descreveram o VO_2 pico como um preditor de mortalidade em uma coorte de pacientes com IC e também incluíram nas análises o V_E/VCO_2.

Nesse estudo, o V_E/VCO_2 foi considerado um marcador de prognóstico mais poderoso do que o VO_2 pico para predizer mortalidade.

Um V_E/VCO_2 menor do que 30 é considerado como uma resposta adequada ao exercício em pacientes com IC e estaria associado a menor risco de mortalidade[37]. Também pode ser definido um ponto de corte maior ou igual a 34 como resposta normal ou anormal do V_E/VCO_2, ou ainda, podem ser considerados quatro níveis de classificação: <30 o grupo com melhor desempenho, 30 a 40 uma classificação intermediária e acima de 40 o grupo com pior eficiência ventilatória[60,61].

Alguns estudos compararam o VO_2 pico e o V_E/VCO_2 para verificar qual seria o marcador com maior poder para predição de mortalidade e hospitalizações na IC[62]. Uma revisão publicada por Arena e colaboradores[37] demonstrou que, na maioria dos estudos que investigaram ambos os marcadores, o V_E/VCO_2 se demonstrou superior ao VO_2 pico como marcador prognóstico. Porém, ambas as variáveis permanecem sendo estudadas e não há consenso sobre qual seria a melhor preditora.

2.2.1. Modificações nos fatores prognósticos relacionados ao exercício

Algumas características do tratamento e dos pacientes podem influenciar as variáveis cardiopulmonares avaliadas na IC. Após o surgimento dos beta-bloqueadores, estes fármacos se tornaram uma terapia padrão para os pacientes com IC[1] e o uso desse medicamento demonstrou reduzir os valores de V_E/VCO_2, sem alterar os valores de VO_2 pico[63-65]. Estudos mais antigos tendem a não reportar o uso de beta-bloqueadores, enquanto que os mais atuais passaram a descrever esta característica nas amostras incluídas. Um estudo de Corrá e colaboradores[66] demonstrou que somente o VO_2 pico, e não o V_E/VCO_2, foi preditor de risco para mortalidade em um subgrupo de pacientes que utilizava beta-bloqueadores. Por outro lado, também existem evidências de que pacientes com valores de V_E/VCO_2 acima de 40 apresentam pior prognóstico independente do uso de beta-bloqueadores[67].

A maioria dos estudos que investigaram valores prognósticos para VO_2 pico e V_E/VCO_2 utilizou predominantemente amostras masculinas[37], apesar da prevalência da IC se demonstrar similar quando comparados homens e mulheres[68]. Guazzi e colaboradores[69] investigaram tanto o VO_2 pico quanto o V_E/VCO_2 de forma separada em homens e mulheres com IC. O VO_2 pico foi mais baixo nas mulheres (13±4 x 17±6 $ml.kg^{-1}.min^{-1}$, p<0,001) e o V_E/VCO_2 mais alto (37±9 x 33±8, p<0,001), o que demonstra uma possível influência do sexo nos resultados que envolverem a análise dessas variáveis. Também existem evidências de que o aumento da idade pode estar associado a aumentos no V_E/VCO_2, em ambos os sexos[70].

A avaliação do VO_2 pico e do V_E/VCO_2 é tipicamente realizada tanto em cicloergômetro, quanto em esteira rolante[71], e não existe um consenso sobre qual a modalidade de teste ou treino seria a mais indicada para avaliar ou treinar os pacientes com IC[37]. Nas Américas, a esteira rolante é o ergômetro mais utilizado no contexto clínico para a avaliação da aptidão cardiorrespiratória dos pacientes[46].

Uma variabilidade de 3 a 4% nos resultados do TCPE é considerada biológica e intrínseca ao teste[46]. Porém, a modalidade de teste pode influenciar a resposta do paciente ao exercício além desta variabilidade considerada fisiológica[59]. Witte & Clark[72] demonstraram que tanto o VO_2 pico quanto o V_E/VCO_2 foram menores no TCPE realizado em cicloergômetro, quando comparado com a esteira, em pacientes com IC. Desde 1961, existem evidências de que um mesmo sujeito atinge valores mais baixos de VO_2 pico, FC máxima e LV_1 mais baixos no TCPE realizado em cicloergômetro, quando comparado a esteira[26-32,73]. Por outro lado, também existem estudos que demonstraram uma associação consistente da aptidão cardiorrespiratória medida pelo cicloergômetro e pela esteira rolante[74,75]. Lembrando que o desejável é que o protocolo de TCPE utilizado possa ser o mais semelhante possível com o ambiente de treinamento do sujeito[46,25].

2.3. Prescrição e efeitos do exercício em pacientes com IC

Enfatiza-se que uma prescrição apropriada de volume (quantidade, duração) e intensidade de esforço é determinante para que o paciente alcance os benefícios esperados pela intervenção de treinamento físico na IC[76]. Diversas recomendações indicam que a prescrição ótima de exercício físico deve ser determinada a partir de uma avaliação objetiva do indivíduo ao exercício, o que inclui observações da FC e do VO_2, entre outros parâmetros[55,56,77].

Portanto, os resultados do TCPE são amplamente utilizados para a prescrição de intensidades de exercício durante o treinamento aeróbico[76,78]. Neste cenário, o VO_2 pico, assim como o primeiro LV_1) têm sido utilizados como pontos de referência para a prescrição[76,79,80]. O exercício aeróbico é tipicamente realizado em uma intensidade de moderada a alta, em um estado de equilíbrio do rendimento energético aeróbico, o que permite a realização de sessões prolongadas de exercício[76].

Indivíduos expostos ao exercício aeróbico, realizado em um mesmo percentual do VO_2 pico ou uma mesma classificação da percepção subjetiva do esforço, apresentam um desempenho mais elevado na esteira do que no cicloergômetro[24]. Sabe-se que a ativação muscular e o déficit do VO_2 se modificam nas diferentes posições corporais que a pessoa precisa adotar para executar um exercício[81,82]. Por outro lado, existe controvérsia quanto a influência que diferentes modalidades de teste podem ter na avaliação dos LV_1, principalmente, se considerada a aptidão cardiorrespiratória dos pacientes (pessoas com melhores resultados apresentariam menores diferenças entre os testes)[83,84]. Desta forma, apesar das indicações para utilizar uma mesma modalidade de teste e treino com os pacientes[25,46], ainda está em aberto a hipótese de que modalidades diferentes de exercício podem influenciar os resultados do teste e treino dos indivíduos.

2.3.1 Efeitos do treinamento no VO_2 pico, V_E/VCO_2, FC máxima e LV_1 em pacientes com IC: resultados de revisões sistemáticas

Revisões sistemáticas demonstraram os efeitos de programas de reabilitação cardíaca com ênfase em exercício sobre a aptidão cardiorrespiratória, hospitalizações e mortalidade na IC, entre outros desfechos[5-15]. Detalhes de todas as revisões citadas a seguir podem ser encontrados no Apêndice 1 do presente documento.

Nas 10 RSMA[5-13,22] que avaliaram os efeitos de intervenções baseadas em exercício sobre o VO_2 pico, a maioria confirmou a hipótese de que o exercício poderia melhorar este marcador prognóstico na IC (Tabela 1). A única RSMA que não demonstrou diferença relacionada aos efeitos do exercício foi a de Chen e colaboradores[10] que incluiu exclusivamente indivíduos com 60 anos ou mais.

Tabela 1. Resultados das revisões sistemáticas com meta-análise que investigaram os efeitos do exercício no pico do consumo de oxigênio em pacientes com insuficiência cardíaca.

Primeiro autor (ano)	Total de pacientes	Efeito global, VO_2 pico (IC 95%)
Smart N (2004) [5]	-	16,5% (14,3% – 18,7%)
Rees K (2004) [6]	569	2,16 $ml.kg^{-1}.min^{-1}$(1,49 - 2,82)
van Tol BA (2006) [7]	1240	2,06 $ml.kg^{-1}.min^{-1}$ (p < 0,001)
van der Meer S (2012) [8]	2.245	1,85 $ml.kg^{-1}.min^{-1}$ (0,75 – 2,94)
Ismail H (2013) [9]	136	1,27 $ml.kg^{-1}.min^{-1}$ (0,85 – 1,70)
Chen YM (2013) [10]	102	0,70 (-0,19 – 1,59)*
Ismail H (2013/2014) [11,22]		
Intensidade: Alta	114	3,33 $ml.kg^{-1}.min^{-1}$ (0,53 – 6,13)
Vigorosa	3.420	2,27 $ml.kg^{-1}.min^{-1}$ (1,70 – 2,84)
Moderada	779	2,17 $ml.kg^{-1}.min^{-1}$ (1,34 – 2,99)
Baixa	70	1,04 $ml.kg^{-1}.min^{-1}$ (-2,5 – 4,57)
Lewinter C (2015) [12]	-	0,98 (0,59 – 1,37)**
Vromen T (2016) [13]	2.235	2,10 $ml.kg^{-1}.min^{-1}$ (1,34 – 2,88)

Legendas e símbolos: IC95% - intervalo com 95% de confiança; * A revisão sistemática com meta-análise incluiu pacientes com no mínimo 60 anos e não definiu a unidade de medida do pico de consumo de oxigênio de pico; ** A medida de efeito foi padronizada para incluir resultados como tempo de exercício, pico de consumo de oxigênio e teste de caminhada de 6 minutos.

A RSMA de Ismail H e colaboradores[9] foi a primeira a demonstrar uma análise de sensibilidade que levou em consideração o tipo de ergômetro utilizado nos estudos originais. Em estudos que utilizaram exclusivamente cicloergômetro o VO_2 apresentou uma melhora de 1,94 $ml.kg^{-1}.min^{-1}$ (IC 95% 1,26 – 2,62).

Outro aspecto levado em consideração em RSMA anteriores foi o uso de exercício aeróbico vigoroso em treinamento intervalado comparado com exercício moderado em treinamento contínuo. Haykowsky e colaboradores[85] conduziram MA a partir dos estudos que compararam essas duas formas de treinamento e demonstraram que o exercício intervalado resultava em maior benefício para o VO_2 pico dos pacientes com IC (2,14 IC 95% 0,66 – 3,63). Categorizando as intensidades, independente do formato do treinamento, Ismail e colaboradores[11,22] sugerem que maiores intensidades podem estar associadas a maiores benefícios no VO_2 pico (Tabela 1).

Quatro estudos[5,11,13,22] exploraram variáveis referentes à frequência, duração e tempo total do programa de treinamento. Porém, um estudo não apresentou os resultados das informações discutidas e dois estudos, oriundos de um mesmo grupo, realizaram subanálises apenas categorizando as características dos protocolos de treinamento, sem realizar testes que buscassem estabelecer relações de dose-resposta entre os parâmetros e o VO_2 pico[5,11,22]. Por fim, o quarto estudo que explorou estas variáveis realizou meta-regressões para tentar estabelecer uma dose-resposta entre os parâmetros de treinamento e o desfecho VO_2 pico. Porém, esta última RSMA, falhou na busca e/ou elegibilidade dos estudos, não incluindo todos os estudos publicados da área e deixando de excluir estudos que não se encaixavam nos critérios propostos pelos autores[13].

Conforme mencionado anteriormente, o V_E/VCO_2 também é considerado como um dos principais marcadores prognósticos relacionado ao exercício na IC[37]. Apesar do pequeno número de ECRs que avaliaram os efeitos do exercício nessa variável, duas RSMA demonstraram os benefícios do exercício por meio de uma redução no V_E/VCO_2 com resultados que variaram de -3,14

(IC 95% -4,81 - -1,47, n=72) a -6,55 (IC 95% -7,24 - -5,87, n=117), ambas melhorando a eficiência ventilatória dos pacientes[9,86].

O benefício do exercício sobre a FC máxima foi demonstrado por meio de uma RSMA que incluiu 683 pacientes oriundos de 18 estudos[7]. Os pacientes apresentaram uma melhora na resposta cronotrópica, com aumento de 3,5 bpm, o que representou 2% em comparação ao valor basal da FC medida em TCPE. O mesmo estudo avaliou os efeitos do exercício sobre o LV dos pacientes com IC (n=511), demonstrando um melhora de 17% em relação ao valor basal.

2.3.2 Efeitos do exercício sobre a mortalidade e hospitalizações

Os estudos sobre as associações entre o treinamento e mortalidade na IC foram marcados, principalmente, por quatro publicações de dois grupos de pesquisa [21,87-89]. O primeiro estudo demonstrou que pacientes submetidos ao treinamento aeróbico apresentavam menores taxas de mortalidade cardíaca em um ano do que pacientes que não realizaram exercício [Redução absoluta de risco (RAR): 23%; RR: 0,37 (0,17-0,84)], assim como de hospitalizações devido a IC [RAR: 19%; RR: 0,29 (0,11 – 0,84)][87]. Um segundo estudo, do mesmo grupo, com 10 anos de acompanhamento, corroborou com os achados anteriores e demonstrou que a mortalidade cardíaca era menor no grupo treinado [RAR: 10%; RC: 0,68 (0,30 – 0,82)], assim como as hospitalizações devido a IC [RAR: 29%; RC 0,64 (0,34 – 0,81)][88]. Por outro lado, resultados do HF-ACTION acenderam o debate sobre os efeitos do treinamento na redução de desfechos clínicos duros[89]. O referido estudo incluiu mais de 2 mil pacientes e, em uma análise inicial, demonstrou que o grupo treinado não apresentava benefícios quanto a redução de mortalidade ou hospitalizações em comparação aos controles [RAR: 3%; RC: 0,93 (0,84 – 1,02)][89]. Porém, quando realizada uma subanálise que ajustada de acordo com o volume de exercício que de fato foi realizado, os pacientes que realizaram de 3 a 7 MET-hora/semana de exercício apresentaram uma redução de 31 a 37% nas taxas de mortalidade ou hospitalizações do que os pacientes que realizaram 1 MET-hora/semana[21].

Podemos observar na Tabela 2 que a maioria das revisões não confirmou a hipótese de que as intervenções baseadas em exercícios estariam associadas a uma menor taxa de eventos (hospitalizações e mortalidade por qualquer causa). Assim, apesar dos resultados que as intervenções baseadas em exercício demonstraram nos marcadores prognósticos da IC, os mesmos benefícios nem sempre se refletiram em redução nas taxas de mortalidade e hospitalizações[5,6,10,12,14-17].

Tabela 2. Resultados das revisões sistemáticas com meta-análise que investigaram os efeitos do exercício nas hospitalizações e mortalidade em pacientes com insuficiência cardíaca.

Primeiro autor (ano)	**Hospitalização**		**Mortalidade**	
	Total de pacientes	Efeito global (IC 95%)	Total de pacientes	Efeito global (IC 95%)
Smart N (2004) [5]	-	-	729	OR 0,61 (0,37 – 1,02)
Rees K (2004) [6 ¥]	659	RR 0,79 (0,09 – 0,85)	962	RR 1,02 (0,70 – 1,51)
ExTraMatch (2004) [14]	-	-	801	HR 0,65 (0,46 – 0,92)
Davies EJ (2010) [15]		OR		OR
Até 12 meses	659	0,79 (0,58 – 1,07)	962	1,03 (0,70 – 1,53)
12 meses ou mais	2.658	0,96 (0,90 – 1,02)	328	0,91 (0,78 – 1,06)
Chen YM (2013) [10]	96	RR 0,73 (0,36 – 1,45)	479	RR 1,01 (0,47 – 2,15)
Lewinter C (2015) [12]	3.585	RR 0,65 (0,50 – 0,84)	4.162	RR 0,88 (0,77 - 1,02)
Taylor RS (2014) [16]		RR		RR
Até 12 meses	1.328	0,75 (0,62 – 0,92)	1.871	0,93 (0,69 – 1,27)
12 meses ou mais	2.722	0,92 (0,66 – 1,29)	2.845	0,88 (0,75 – 1,02)
Sagar VA (2015) [17]		RR		RR
Até 12 meses	1.328	0,75 (0,62 – 0,92)	1.871	0,93 (0,69 – 1,27)
12 meses ou mais	2.722	0,92 (0,66 – 1,29)	2.845	0,88 (0,75 – 1,27)

Legendas e símbolos: IC 95% intervalo com 95% de confiança; OR: *odds ratio*; RC: razão de chance; RR: risco relativo; ¥ O estudo mensurou apenas mortalidade por causa cardíaca.

2.4. Sumário de evidências

As evidências apontam que o exercício físico melhora marcadores de prognóstico na IC (VO_2 pico e V_E/VCO_2). Porém, quando avaliada diretamente mortalidade e hospitalizações, ainda existe controvérsia quanto aos seus benefícios. Características dos protocolos de treinamento (maiores intensidades) e do perfil dos pacientes (sexo, uso de beta-bloqueadores) parecem estar associadas positivamente aos resultados obtidos com o exercício físico. Por outro lado, ainda se fazem necessárias novas investigações para testar a associação de demais características com desfechos importantes na IC.

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Capítulo III

3. Objetivo geral

Sumarizar evidências de ECRs com fins de avaliar os efeitos de diferentes protocolos de exercício e das características dos pacientes no VO_2 pico, V_E/VCO_2, FC máxima, primeiro LV, mortalidade e hospitalizações em pacientes com IC e FE reduzida submetidos ao treinamento aeróbico.

3.1. Objetivos específicos

- Conduzir uma RSMA de ECRs com geração de síntese quantitativa dos efeitos do treinamento aeróbico sobre os valores de VO_2 pico, V_E/VCO_2, FC máxima, primeiro LV, mortalidade e hospitalizações;

- Identificar características potencialmente preditoras dos protocolos de exercício e dos pacientes e suas associações com as variações em VO_2 pico, V_E/VCO_2, FC máxima, primeiro LV;

- Identificar características dos protocolos de exercício e dos pacientes associadas com VO_2 pico, V_E/VCO_2, FC máxima, primeiro LV.

CAPÍTULO IV

4. Artigo

Association of exercise variables and clinical characteristics with effects of aerobic training in heart failure with reduced ejection fraction: a dose-response systematic review and meta-analysis

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Association of exercise variables and clinical characteristics with effects of aerobic training in heart failure with reduced ejection fraction: a dose-response systematic review and meta-analysis

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WHAT IT ALREADY KNOW ON THIS TOPIC

Exercise training is an evidence-based intervention for improvements in cardiorespiratory fitness and quality of life in heart failure patients. Pooled data has shown that reductions in the risk of mortality and hospitalization were achieved for patients attaining a minimum of 3-5 metabolic equivalent-hour per week, demonstrating that training characteristics may influence the benefits.

WHAT THIS STUDY ADD

The available evidence suggests that improvements promoted by aerobic exercise training in peak oxygen uptake (VO_2) were independent of age, sex distribution within the study groups, ejection fraction, beta-blockers, modality of training, supervised session, and intention-to-treat analysis in heart failure with reduced ejection fraction patients.

In addition, samples with New York Heart Association class I-III and protocols that controlled the exercise intensity were associated with improvements of peak VO_2.

The benefits on peak VO_2 presented positive correlations with maximal prescribed intensity and volume of training.

ABSTRACT

OBJECTIVE

To summarise the association of methodological characteristics and clinical variables related to the effects in cardiorespiratory fitness promoted by chronic aerobic exercise in HF with reduced ejection fraction (HFrEF).

DESIGN

Systematic review with meta-analysis and meta-regressions of randomised controlled trials (RCTs).

DATA SOURCES

We searched MEDLINE via PubMed, EMBASE, and Cochrane up to November 2015.

STUDY SELECTION

RCTs of aerobic exercise training of at least 4 weeks for HFrEF (PROSPERO CRD42015025075). We extracted clinical data, risk bias, testing and training characteristics. The outcomes were peak oxygen uptake (VO_2), ventilation / carbon dioxide production (V_E/VCO_2), maximal heart rate (HR), first ventilatory threshold (VT), all-cause and cardiovascular mortality, and hospitalization. The main analyses were generated by random models and were followed by subgroup and sensitivity analyses, meta-regressions, and weighted correlations.

RESULTS

Our search identified 31.721 references, of which 35 RCTs were included (N=3.939 patients). Aerobic exercise was associated with an improvement of peak VO_2 (weighted mean difference - WMD 3.23ml.kg^{-1}.min^{-1}, CI 95% 2.63-3.83, V_E/VCO_2 (WMD -2.43, -4.47 - -0.39), maximal HR (WMD 3.36bpm, 0.61-6.11), and 1st VT (WMD 2.97ml.kg^{-1}.min^{-1}, 2.18-3.76). Heterogeneity was significant and superior than 75% for these outcomes. Increases in peak VO_2 were independent of exercise modalities and dependent of maximal targeted

intensities. Characteristics of protocols and patients are mostly associated with changes on V_E/VCO_2 and maximal HR. In a multivariable meta-regression model, adjusted for age, EF and training volume the maximal intensity target intensity was associated with improvements of peak VO_2 (coefficient = 0.121, 95% CI = 0.046-0.196, p = 0.033).

CONCLUSIONS

Aerobic exercise training associated with increases in peak VO_2, which occurred even in stratified analyses accounting for age, sex, cardiac contractility, beta-blockers, training mode, exercise supervision, and intention to treat analysis among RCTs with HFrEF. However, NYHA functional classes and exercise intensity showed association with benefits in cardiorespiratory fitness, underscoring the need for exercise prescriptions based on the individual characterization and exercise progression.

Introduction

Improvements in clinical management have lengthened survival and reduced hospitalization in patients with chronic heart failure (HF), however, clinical outcomes remain unsatisfactory.[1] European results demonstrate that 12-month rates for stable/ambulatory HF patients were, respectively, 7% and 32% for all-cause mortality and hospitalization.[2]

All-cause mortality is generally higher in HF with reduced ejection fraction (HFrEF) than preserved ejection fraction (EF).[2 3] In addition, exercise intolerance is a frequent symptom of HFrEF and one major treatment goal is to improve exercise capacity.[4] Therefore, exercise training is a component of rehabilitation programmes for this population,[5 6] being recognized as evidence class I for HF treatment.[7] On the other hand, there is no consensus as to which protocols (modality, frequency, volume, intensity) are the best predictors in the treatment of HFrEF patients.[8]

Clinical value of markers from cardiopulmonary exercise testing are clinically useful and widely used to patients with HF.[1 9] The prognostic value of peak oxygen consumption (VO_2) in HF patients referred for heart transplant supported cardiopulmonary exercise testing as component in the management of HF treatment.[10] Peak VO_2 and V_E/VCO_2 are recommended for identification of high-risk patients,[8] because they are strongly related to prognosis in HF independent of age, EF and therapy with ß-blockers.[9 11 12] Even a small increase of 6% for peak VO_2 was related with lower risk for HFrEF hospitalization, cardiovascular mortality, and all-cause mortality.[13] Also, maximal heart rate (HR) and ventilatory threshold (VT) are variables usually improved by exercise training, and are commonly used as parameters for exercise prescription.[14] Some exercise training variables as well several clinical characteristics should be considered in this scenario. In this regard, amount of exercise or sex could contribute, or at least be confounding factors related with effects from intervention studies. The largest randomised controlled trial (RCT) that investigated effects of exercise training for HFrEF patients (HF-ACTION) demonstrated that subgroups who achieved a moderate target for exercise training prescription (3-7 metabolic equivalent-hour per week) presented reduction of all-cause mortality or hospitalization compared to those who did not achieve such exercise dosage.[15] Studies have tried into added utility of high-intensity exercise when compared to low-moderate-intensity levels and have showed beneficial effects for the patients.[16] Among several published systematic review and meta-analysis (SRMA) regarding exercise and HF,[14 17-24] only three have explored hypotheses involving exercise characteristics (program length, sessions, duration and/or intensity).[20 23 24] So far, the available pooled data may present equivocal evidence about individual or methodological influence for improvements on peak VO_2, or risk reduction for mortality or hospitalization.

Methodological or clinical characteristics may account for different results in RCTs. In this regard, evidence from the HF-ACTION suggests sex as a factor of interest, since women presented lower risk for mortality and hospitalization than men.[23 25] This is important because women have been poorly represented in previous HF studies[4] and older women may present very low values of peak VO_2.[26] Despite of that, there was not previously SRMA investigating the influence of exercise prescription variables and clinical characteristics together in effects of aerobic exercise training for HFrEF patients. The purpose of the investigation was to summarise the effects of aerobic exercise training on peak VO_2, V_E/VCO_2, HR, 1st VT, mortality and hospitalization in HFrEF patients taking into account the variations in both methodological issues such as training protocols and testing ergometers as well as in patients characteristics among several study groups composing retrieved RCTs.

Methods

The study was carried out and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement)[27]. The study registration number on PROSPERO is CRD42015025075.

Search strategy

The following databases were searched up to November 2015: MEDLINE via PubMed, EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. The full search strategy is available at the PROSPERO record. In brief, search terms were adapted from a previous SRMA[20] and included terms as regards: exercise, treadmill, cycle ergometer, heart failure, RCT. Searches were not restricted by language, but studies in other languages than English were excluded during the review process. Reference lists of previously published SRMA and included articles were also examined for additional studies, and grey literature was searched through clinical trial registries (www.controlled-trials.com/isrctn/www.clinicaltrials.gov).

Eligibility criteria

Studies were deemed eligible if they were RCT that included adults (>18 years) with either ischaemic or non-ischaemic aetiology and specified criteria for the diagnosis of HFrEF, such as an objective assessment of left ventricular EF or by clinical findings; receiving aerobic exercise training alone, compared with standard medical care or attention placebo control group, and a minimum follow-up of 4 weeks. Also, they should report at least one sought outcome: peak VO_2, maximal HR, V_E/VCO_2, 1st VT, mortality (all-cause and cardiac), or hospitalization (all-cause, cardiac, or HF-related). We excluded trials that recruited patients with HF with EF > 45%), studies that included only patients using implantable devices, or reports that omitted the exercise protocol as defined as non-available information regarding exercise prescription (exercise type, duration, frequency and/or intensity). If the aerobic exercise training was part of a comprehensive cardiac rehabilitation programme, which are defined as programmes including components such as health education and psychological treatment, the trial was also excluded.

Study selection and data extraction

Full-text papers of all potentially eligible trials were independently assessed by two reviewers and disagreements were resolved by discussion (Figure 1). One half of references were independently assessed by two reviewers (KCB + MMP) and the other half by two others (RPS + CAS), who reviewed titles, abstracts and full texts. All data extraction also had dual review (KCB + MMP or KCB + RPS, one half each pair). When necessary, a third review was required (DU).

Figure 1 |

The following information was extracted from included studies using a standardised proforma: details of the study population and their baseline characteristics, details of the intervention (types of test and training, exercise training intensity and volume, supervision, intensity control) and control group, length of follow-up, and details of outcome results. All data extraction and risk of bias assessment were undertaken by two reviewers (KCB + RPS, KCB + MMP) using a standardized form. When data from outcomes results were not available in each manuscript (exactly values), we contacted 12 authors requesting missing data and received 7 answers (58%). The included studies who had missing necessary data for meta-analyses were kept in our systematic review but excluded from quantitative analyses (n=3).

Assessment of risk of bias

The risk of bias was assessed using the Cochrane tool.[28] We evaluated random sequence generation (all description for randomisation sequence generation), allocation concealment (in advance or during enrolment), blinding of outcome assessment (were considered only the evaluation of outcomes from presented meta-analysis), incomplete outcome data (to assess whether all participants randomised were included in an intention-to-treat analysis and loss-to-follow up), selective reporting (we evaluated whether pre-specified outcomes were reported), and sample size calculation (any sample size calculation).

Statistical analyses

Data from intention-to-treat analyses were entered whenever available in included RCTs. Pooled-effect estimates were obtained by comparing the least squares mean percentage change from baseline to the end of the study for each group, and were expressed as the weighted mean difference (WMD) between group for peak VO_2, V_E/VCO_2, maximal HR, and 1st VT. Calculations were performed using a random-effects and fixed-effects model, and comparisons were made for each outcome, comparing aerobic exercise with a control group.[29 30] For trials in which two exercise interventions were compared with a single control group, we split this shared control group into two groups, with a half sample size.

Statistical heterogeneity of aerobic exercise effect among studies was assessed using Cochran´s Q test (threshold *P* value of 0.1).[31 32] We performed sensitivity analyses to evaluate subgroups of studies most likely to yield valid estimates of the intervention based on prespecified relevant clinical characteristics of patients (% men, age, EF, New York Heart Association - NYHA, and % ß-blockers), characteristics of exercise protocols (intensity control and session supervised) and methodological variables (intention to treat analyses). Second, meta-regression analyses were performed using univariate meta-regression models. We tested some numerical variables (age, % men, mean EF, % using ß-blockers, maximal exercise intensity prescribed, and volume) that could present association with changes in outcomes. In addition, we tested four models combining significant variables with multivariable meta-regression ($p < 0.20$). For each meta-regression model, the adjusted R^2 indicated the proportion of between-study variance explained by variables.[33 34]

In addition, we generated correlations to test the association between changes on peak VO_2, V_E/VCO_2, maximal HR, and 1st VT, and variables tested in the meta-regressions. Publication bias was assessed using a funnel plot of each trial's effect size against the standard error.[35] All analyses of numerical variables were conducted using Stata 11.0 software (Stata, College Station, TX, USA) and all analyses of categorical data were calculated with RevMan 5 (RevMan, The Nordic Cochrane Centre, Copenhagen, Denmark). Graphics were elaborated using Stata 11.0 software (Stata, College Station, TX, USA) or Forest Plot Viewer 1.0.[36]

Patient involvement

No patients were involved in setting the research question, data collection or outcome measures, neither were they involved in design of the study. We have no plans to involve patients in dissemination of results.

Results

Our searches identified 31.721 titles. After title and abstract screening, 31.468 were excluded using predefined criteria resulting in 253 full-text papers for complete assessment. Of these, 35 papers were therefore included in the review (Figure 2).

Figure 2 |

Description of RCT and intervention characteristics

The 35 trials included a total of 3.939 patients. Recruited subjects were mainly HFrEF patients without complications, NYHA class II and III. Mean age ranged from 52 to 75 years, and the proportion of males ranged from 60% to 100% (Table 1). Almost all trials were exercise-only interventions, just one had one arm of dance intervention that only this arm was not included for presented analyses. Exercise training programmes ranged widely across the studies (Table 2): modality, 71% realized all cardiopulmonary exercise testing with cycle ergometer and 54% was trained by exclusively cycling; overall duration, 4 weeks to 10 years; weekly volume of training, 69 – 1.022 minutes; frequency, 2 - 7 sessions/week; session duration, 15 - 165 minutes; and intensity, mainly by maximal HR (40% to 90%) and peak VO_2 (30% to 80%); 57% controlled intensity during exercise sessions. Exercise was entirely supervised in 23 studies (66%).

Table 1 |

Table 2 |

Peak VO_2, V_E/VCO_2, maximal HR, and 1st VT

All studies assessed peak VO_2 from ergospirometry and were included in our systematic review, but we excluded four articles from meta-analyses of peak VO_2 because they did not provided enough data for that (Table S1). The peak VO_2 was greater when compared aerobic exercise training and control group. Also, there was benefits analysing subgroups prescribed by exclusively walking, cycling or mixed both (Figure 3). Seven studies assessed V_E/VCO_2 during the maximal exercise test with ergospirometry (Table S1), and V_E/VCO_2 improved with aerobic exercise prescription. Studies that used exclusively cycling maintained this benefit (Figure 4). We were not able to meta-analysis the V_E/VCO_2 by walking, because we did not find studies exploring that.

Figure 3 |

Figure 4 |

Seventeen studies assessed maximal HR during the maximal exercise test (Table S1), and maximal HR improved with aerobic exercise training. When analysed the test and training modality, studies that used exclusively cycling were able to keep this improvement (Figure 5). Fifteen studies assessed 1st VT (Table S1), and it improved with aerobic exercise intervention. This improvement was kept for studies that used cycling and mixed both walking and cycling (Figure 6).

Figure 5 |

Figure 6 |

Improvements on peak VO_2 were confirmed in almost all subgroups studied (Figure 7). Evaluating % men, age, EF, % using ß-blockers, use of intention to treat analysis, and session supervised, both arms studied presented improvements of peak VO_2. Also, studies without NYHA IV and with intensity control during all sessions presented benefits for peak VO_2. V_E/VCO_2 decreased in studies with % of men ≤ 90%, mean age > 55 years, without NYHA IV, more than 75% of sample using β-blockers, protocols comprising intensity control, and without supervision in all period of protocol. As shown in Figure 8, maximal HR increased in studies with % of men ≤ 90%, mean EF > 30%, NYHA IV, sample using β-blockers < 75%, with intention to treat analysis, controlling the intensity during sessions, and supervising all sessions. Lastly, 1st VT increases was associated with the same studies characteristics that influenced improvements of peak VO_2.

Figure 7 |

Figure 8 |

Data from RCTs indicated that maximal target for intensity prescribed may explaining the heterogeneity between studies improvements for peak VO_2 (Table 3). Maximal target of intensity prescribed by peak VO_2 presented significant positive association on meta-regression and correlation with improvements of peak VO_2. In addition, weekly training volume presented only positive correlation with improvement of peak VO_2. Improvements on 1st VT also presented association and correlation between their improvements with training volume. In a multivariate meta-regression model, adjusted for age, EF and training volume, the maximal target intensity (prescribed by peak VO_2 or maximal HR) confirmed its association with improvements of peak VO_2 (coefficient = 0.121, 95% CI = 0.046-0.196, p = 0.033) and 1st VT (coefficient =

0.084, 95% CI = 0.006-0.161, p = 0.037). V_E/VCO_2 and maximal HR improvements did not presented correlations with all parameters tested as numerical variables.

Table 3 |

In all 35 studies included, only 5 had mortality and/or hospitalization in outcomes (Table 4). Using fixed-effects models, we did not found association between exercise intervention and all-cause mortality, cardiac mortality, all-cause hospitalization and cardiac hospitalization. When analysed hospitalization due heart failure the aerobic exercise presented benefit for patients (RR: 0.83, 95% CI 0.71-0.97). Using random-effects models, we did not found association between exercise intervention and all variables of mortality and hospitalization.

Table 4 |

As shown in Figure 9, evaluation of selective reporting and incomplete outcome data were parameters with 66% and 63%, respectively, of low risk of bias in all 35 studies included. After them, random sequence generation presented 40% of studies in low risk of bias. Blinding of outcome assessment (20%), sample size calculation (20%), and allocation concealment (9%) presented few studies with low risk of bias.

Figure 9 |

Funnel plots demonstrated an asymmetry in the analysis of all studies that measured peak VO_2, V_E/VCO_2, maximal HR and 1st VT (Figure 10). Low number of studies in the down area indicates a publication bias.

Figure 10 |

Discussion

The key findings from this SRMA include description of patients and training characteristics associated with improvements in cardiorespiratory fitness for patients with HFrEF. The present evidence synthesis indicates that characteristics as sex, age, NYHA, use of ß-blockers, intensity control, maximal target intensity and training volume could change the effects of aerobic exercise training demonstrated by RCTs. Extending the knowledge on factors associated with benefits promoted by chronic aerobic exercise may improve tailored exercise prescriptions and future research for HFrEF patients.

This SRMA was conceived to explore the effects of aerobic exercise training stratified by modality of test and training. To our knowledge, a previous SRMA has shown a sensitivity analysis including only studies with cycle ergometer maximal exercise test, however, this analysis was secondary to a specific appraisal on exercise training for patients using different types of beta-blockers.[21] Another SRMA demonstrated that studies with aerobic interval training (frequently associated with higher intensities) were more effective than continuous aerobic training to improve peak VO_2.[18] Additionally, exercise levels from moderate to high intensities presented larger increases in peak VO_2, with a dose dependent pattern related to intensity.[20] On the other hand, they also informed that volume of exercise may be a confounder in their results. We evaluated the association of prescribed intensity with improvements in peak VO_2 and found positive association, independently of age, EF and training volume, and 49% of improvements in peak VO_2 were associated with maximal intensity prescribed.

Despite the HF being a condition affecting primarily the elderly population, most of studies included few patients being 70 years or older. Our results exploring age differences demonstrated that studies with sample mean age more than 55 years presented improvements in peak VO_2 not differently than samples with 55 years or less. Also, we demonstrated that improvements in peak VO_2 are not correlated with mean age of patients. A RCT included 27 older patients (75±11years) to either aerobic interval training (95% of maximal HR), moderate continuous training (70% of maximal HR) or control group, three times per week for 12 weeks.[37] The main finding in this study was that aerobic interval training was safety and superior, when compared with moderate continuous training with regard to aerobic capacity in old patients. Therefore, this finding supports that higher intensity training for older population with HF probably are safety and associated with greater improvements of peak VO_2.

Despite only seven RCT analysing the effect of exercise training on V_E/VCO_2, for this variable we were able to include patients with NYHA ranging from I to III, mean age between 55 and 64 years old, with a maximum of 24% of women as sample. One of our seven samples was obtained directly with main author and it is not reported in the original paper.[38] Evaluating individual studies characteristics, the three original papers demonstrating improvement in V_E/VCO_2, were the same one with more women between these seven (15 to 24%). In addition, three from four that did not demonstrated improvements had 100% of men as sample. It is in agreement with insights suggesting that low women sample, or no one in these cases, may underestimate the improvement based on exercise interventions for HF.[4] Our results are in accordance with previously published meta-analysis showing significant reduction in V_E/VCO_2, with only four studies included.[21] [22] Despite the lower number of studies including V_E/VCO_2 (7), than peak VO_2 (31), the literature already demonstrate that aerobic capacity (peak VO_2) and ventilatory efficiency (V_E/VCO_2) provide prognostic value for clinical outcomes and are responsive to a multiple HF treatments.[12]

According study realised to verify the agreement between training mode in cardiac patients demonstrated that modality of cardiopulmonary exercise test has a potential impact on VT results.[39] In our sub analyses studies that mixed cycling and walking for test/training demonstrated benefits on 1st VT as also studies that used only cycle ergometer for test and training. In other hand, studies involving treadmill test and training were not able to confirm improvements on 1st VT. These different responses may be due a muscle activation and ventilatory efficiency during different exercise modalities.[40-42]

In this review, we found few studies intervening exclusively with aerobic exercise prescription and testing clinical benefits in death and hospitalizations. The literature already demonstrated that exercise training results in reduction of clinical events. Adherent patients have greater benefits and it is associated with exercise volume measured by the product of intensity prescribed and the hours of exercise per week.[15] [16] Complementing that, we demonstrated that improvements in an important prognostic marker (VO_2) are associated with maximal intensity prescribed, without apparent influence by age, EF and week training volume measured by hours per week. Also, the available evidence of aerobic exercise training demonstrated benefits in hospitalizations due to HF.

Limitations

As with any investigation, there are limitations. We demonstrated that all studies describing sex characteristics (n=32) presented more than a half of men, from these, 41% included only men in their sample. So, our results are mainly based in men results, and it is already described the importance of pay attention for limitations (external validity) from published studies for women's treatment.[4] HF-ACTION subanalyses presented evidence that exercise training is associated with larger reduction in all-cause mortality and hospital stay in women than in men, despite the absence of difference in improvements on peak VO_2 when compared both sex.[25] So, because only 11% of studied samples are women, results presented here may be underestimating the benefits for women's treatment. Due to this, we encourage new studies which will emphasize adding woman on sample.[4] We found few studies of exclusively aerobic exercise intervention measuring deaths or hospitalizations. Despite of that, our main objective was demonstrating the characteristics associated with two important prognostic markers in HF. Taylor and collaborators (2015) already demonstrated that studies with exercise only (without comprehensive programs of cardiac rehabilitation) and studies with aerobic training alone are not associated with differences in results of death and hospitalizations in their SRMA involving all types of interventions with exercise for HF patients.[23] Lastly, the mean age of the patients in our SRMA was mostly less than 60 years of age which highlights the need to more thoroughly examine the role of exercise in older persons with HF.

Conclusion

Aerobic exercise training associated with increases in peak VO_2, which occurred even in stratified analyses accounting for age, sex, cardiac contractility, beta-blockers, training mode, exercise supervision, and intention to treat analysis among RCTs with HFrEF. However, NYHA functional classes and exercise intensity showed association with benefits in cardiorespiratory fitness, underscoring the need for exercise prescriptions based on the individual characterization and exercise progression. These results agree with the recommendations that include exercise training as an adjunctive treatment for HF. It could be prescribed as walking, cycling or both, but some characteristics of patients and training should be considered before planning the expected results.

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Tables

Table 1 | Characteristics of studies and patients included in the systematic review.

First Author	Country	Publication year	Sample size	Sex distribution (%)	Age (mean)	NYHA class included	Cut point for LVEF	LVEF (mean)	Aetiology	Peak VO_2 ($ml.kg^{-1}.min^{-1}$, mean)	Maximal HR (bpm, mean)
Adamopoulos S	Greece	2002	48	NR	55	II-III	14-35%	23	Ischaemic or idiopathic dilated cardiomyopathy	16.2	NR
Belardinelli R	Italy	1995	55	85/15	55	II-III	<25%	27	Ischaemic or idiopathic	15.6	137
Belardinelli R	USA	1996	43	88/12	55	I-III	<30%	27.5	Ischaemic cardiomyopathy	15.5	136
Belardinelli R	Italy	1999	99	89/11	59	II-IV	≤ 40%	28	Ischaemic or idiopathic dilated cardiomyopathy	15.5	137
Belardinelli R	Italy	2008	86	85/15	59	II-III	< 40%	36	NR	16.3	130
Belardinelli R	Italy	2012	123	78/22	59	II-III	<40%	37	Ischaemic or nonischaemic	NR	NR
Braith RW	USA	1999	19	NR	62	II-III	<40%	30	Ischaemic	13	NR
Callaerts-Végh Z	USA	1998	17	100/0	54	NR	<40%	33	Ischaemic	19.13	141
Collins E	USA	2004	31	100/0	64	I-III	≤ 40%	29	NR	17.05	NR
Corvera-Tindel T	USA	2004	79	99/1	63	II-IV	≤ 40%	27	Ischaemic and nonischaemic	14.25	119

Dehkordi AH	Iran	2015	61	67/33	69	II-III	≤ 40%	32	Ischaemic or idiopathic dilated cardiomyopathy	17.5	NR
Dubach P	USA	1997	25	100/0	55	NR	<40%	32,4	Ischaemic	19.1	142
Dziekan G	USA	1998	20	100/0	55	II-III	<40%	28,9	NR	18.75	143
Eleuteri E	Italy	2013	21	100/0	65	II	≤ 40%	29	Ischaemic or idiopathic dilated cardiomyopathy	15.8	NR
Fu T	China	2013	45	64/36	67	II-III	≤ 40%	38,3	Ischaemic. hypertensive and cardiomyopathy	16.47	135
Gottlieb SS	USA	1999	33	88/12	66	II-III	<40%	22	Ischaemic and primary	14	NR
Hambrecht R	Germany	1998	20	100/0	55	II-III	≤ 40%	24	Dilated cardiomyopathy	17.95	NR
Keteyian SJ	USA	1999	51	100/0	56	II-III	≤ 35%	22	Ischaemic or non-ischaemic	15.35	132
Keyhani D	Iran	2013	70	60/40	61	II	≤ 35%	32	NR	5.15	130
Kiilavuori K	Finland	1995	20	95/5	52	II-III	< 40%	24	Ischaemic or idiopathic dilated cardiomyopathy	19.8	NR
Kiilavuori K	Finland	1996	27	96/4	52	II-III	<40%	24	Idiopathic dilated or ischaemic cardiomyopathy	18.8	NR
Klecha A	Poland	2007	50	76/24	60	II-III	≤ 35%	28	Ischaemic	14.7	123

Klocek M	Poland	2005	42	100/0	56	II-III	<40%	34	Ischaemic	15.47	111
Linke A	Germany	2001	22	100/0	58	II-III	<40%	25	Ischaemic heart disease or dilated cardiomyopathy	16.45	NR
Mezzani A	Italy	2013	30	100/0	64	2.1±0.4	≤ 40%	29	Ischaemic or dilated cardiomiopathy	16.3	123
Mueller L	USA	2007	50	100/0	55	NR	<40%	NR	Ischaemic and non-ischaemic	19.9	147
Myers J	USA	2001	24	100/0	55	II-III	<40%	32	Ischaemic	19.05	144
Myers J	USA	2012	50	100/0	55	II-III	<40%	33	Ischaemic or nonischaemic	19.84	147
O'Connor CM	USA	2009	2331	72/28	59	II-IV	≤ 35%	25	51% ischaemic	14.45	NR
Passino C	Italy	2006	95	78/22	60	I-III	<45%	34	Idiopathic or postischaemic	14.5	NR
Passino C	Italy	2008	97	86/14	61	I-III	<45%	35	Idiopathic or ischaemic	14.75	NR
Quittan M	Austria	1999	27	88/12	55	II-III	<30%	18	Dilated idiopathic cardiomyopathy	16.85	NR
Sarullo FM	Italy	2006	60	75/25	53	II-III	<40%	29	Ichaemic hypertensive or idiopathic	14.65	NR
Wisloff U	Norway	2007	27	74/26	75	NR	<40%	29	Ischaemic	13.1	130
Yaylalt YT	Turkey	2015	41	85/15	61	II-III	30-45%	NR	Ischaemic or non-ischaemic	14.33	119

NYHA = New York Heart Association; LVEF = Left ventricular ejection fraction; VO_2 = Oxygen uptake; HR = Heart rate; NR = Not reported.

Table 2 | Characteristics of exercise interventions and outcomes.

Study		Exercise modality		Session					
First Author	Year	Test mode	Training mode	Intensity prescription	Duration (min/session)	Frequency (times/week)	Duration (weeks)	Intensity control	Supervision
Adamopoulos S	2002	W	C	60-80% peak HR	30	5	12	Yes	No
Belardinelli R	1995	C	C	60% of peak VO_2	40	3	8	Yes	Yes
Belardinelli R	1996	C	C	60% peak VO_2	40	3	8	?	Yes
Belardinelli R	1999	C	C	60% peak VO_2	40	2 to 3	56	Yes	Yes
Belardinelli R	2008	C	W + C	70% peak VO_2	30	3	8	Yes	Yes
Belardinelli R	2012	C	W + C	60-70% peak VO_2	40	2 to 3	520	Yes	Both
Braith RW	1999	W	W	40-80% peak VO_2	10-45	3	16	Yes	Yes
Callaerts-Végh Z	1998	C	W + C	60-70% reserve HR	120-165	7	8	Yes	Yes
Collins E	2004	W	W	50-70% peak VO_2	45-50	3	12	?	Yes
Corvera-Tindel T	2004	C	W	40-65% maximal HR	10-60	5	12	?	Both
Dehkordi AH	2015	?	W	60-70% reserve HR	30-35	3	24	Yes	Yes
Dubach P	1997	C	W + C	C: 60-70% reserve HR; W: intensity was stratified into four levels on the basis of clinical status, exercise capacity and performance on test	120-165	7	8	Yes	Yes
Dziekan G	1998	C	W + C	C: 60-80% reserve HR; W: intensity was stratified into four levels on the basis of clinical status, exercise	120-165	7	8	?	Yes

				capacity and performance on test					
Eleuteri	2013	C	C	Anaerobic Threshold	30	5	12	Yes	No
Fu T	2013	C	C	Continuous: 30-60% peak VO_2; Interval: 30-80% peak VO_2	33-36	3	12	Yes	Yes
Gottlieb SS	1999	W	W + C	Borg scale 12-13	C: 4572 meters; W: 9144 meters	3	24	?	Yes
Hambrecht R	1998	C	C	70% HR at peak VO_2	40-60	6	24	?	Both
Keteyian SJ	1999	C	W + C	50-80% reserve HR	33	3	24	?	?
Keyhani D	2013	W	W	60-80% peak HR	15-30	3	8	Yes	Yes
Kiilavuori K	1995	C	C	50-60% peak VO_2	30	3	12	?	Yes
Kiilavuori K	1996	C	C	50-60% peak VO_2	30	3	12	?	Yes
Klecha A	2007	W	C	80% predict HR at peak VO_2	25	3	24	Yes	?
Klocek M	2005	W	C	Constant: 60% maximal HR for age; Progressive: 75% maximal HR for age	25	3	24	?	Yes
Linke A	2001	C	C	70% peak VO_2	60	7	4		Yes
Mezzani A	2013	C	C	1st ventilatory threshold	30	5	12		No
Mueller L	2007	C	W + C	60-80% reserve HR	90-120	7	4		Yes
Myers J	2001	C	W + C	60-70% peak VO_2	120-165	7	8		Yes
Myers J	2012	C	W + C	60-80% reserve HR	120-165	7	8		Yes

O'Connor CM	2009	T + C	W + C	60-70% reserve HR	15-40	3 to 5	36	Both
Passino C	2006	C	C	65% HR at peak VO_2	30	3	36	Both
Passino C	2008	C	C	65% peak VO_2	30	3	36	Both
Quittan M	1999	C	C	50% HR at peak VO_2	50	2 to 3	12	Yes
Sarullo FM	2006	C	C	60-70% peak VO_2	30	3	12	Yes
Wisloff U	2007	W	W	Continuous: 70-75% peak HR; Interval: 50-95% peak HR	38-47	3	12	Both
Yaylalt YT	2015	C	C	50-75% reserve HR	30	3	12	Yes

W = Walking; C = Cycling; ? = Unclear; HR = Heart rate, $\dot{V}O_2$ = Oxygen uptake; Min = minute.

Table 3 | Univariate metaregression and correlations associations with peak VO_2, V_E/VCO_2, maximal HR, and 1st VT.

	Parameters	n	Meta-regression				Correlation	
			Coefficient	95% CI	P	Adjusted R^2	R	p
Peak VO_2	Men (%)	32	-0.008	-0.06 - 0.04	0.741	3%	-0.06	0.741
	Age (years)	34	0.006	-0.09 - 0.10	0.889	-3%	0.02	0.889
	EF (%)	30	0.12	-0.01 - 0.25	0.076	10%	0.33	0.073
	Patients using BB (%)	25	0.004	-0.02 - 0.02	0.698	4%	0.08	0.701
	Intensity based on							
	Peak VO_2	14	0.12	0.03 - 0.21	0.010	50%	0.70	0.005
	Maximal HR	8	0.11	-0.01 - 0.23	0.070	38%	0.67	0.068
	Reserve HR	7	-0.04	-0.54 - 0.46	0.843	-27%	-0.10	0.835
	Training volume							
	By week	33	0.02	-0.00 - 0.003	0.056	8%	0.35	0.043
V_E/VCO_2	Men (%)	7	0.21	-0.003 - 0.42	0.052	65%	0.73	0.059
	Age (years)	7	-0.14	-1.14 - 0.85	0.727	-21%	-0.16	0.726
	EF (%)	7	-0.01	-1.09 - 1.07	0.977	-27%	0.002	0.996
	Patients using BB (%)	7	-0.04	-0.12 - 0.04	0.260	15%	-0.49	0.261
	Intensity based on							
	Peak VO_2	3	-0.67	-14.37 - 13.05	0.651	-59%	-0.53	0.646
	Maximal HR	2	-	-	-	-	-	-
	Reserve HR	1	-	-	-	-	-	-
	Training volume							
	By week	7	0.003	-0.003 - 0.009	0.210	20%	0.54	0.209
Maximal HR	Men (%)	20	-0.05	-0.29 - 0.19	0.671	-3%	-0.12	0.621
	Age (years)	20	-0.13	-0.72 - 0.45	0.639	-6%	-0.11	0.640
	EF (%)	17	0.12	-0.85 - 1.09	0.792	-10%	0.08	0.770
	Patients using BB (%)	12	-0.09	-0.22 - 0.03	0.128	14%	-0.52	0.081

	Intensity based on							
	Peak VO_2	7	0.11	-0.59 - 0.82	0.691	-26%	0.24	0.606
	Maximal HR	4	0.04	-4.06 - 4.14	0.969	-43%	0.03	0.967
	Reserve HR	6	-0.25	-1.95 - 1.46	0.709	0%	-0.21	0.692
	Training volume							
	By week	20	-0.003	-0.01 - 0.005	0.428	3%	-0.19	0.410
First ventilatory threshold	Men (%)	17	0.06	-0.02 - 0.15	0.146	8%	0.36	0.150
	Age (years)	17	-0.10	-0.27 - 0.07	0.237	4%	-0.30	0.236
	EF (%)	17	0.03	-0.24 - 0.31	0.793	-7%	0.08	0.771
	Patients using BB (%)	13	-0.001	-0.04 - 0.03	0.918	11%	-0.03	0.917
	Intensity based on							
	Peak VO_2	9	0.08	-0.02 - 0.19	0.095	26%	0.61	0.082
	Maximal HR	4	0.11	-0.09 - 0.32	0.142	79%	0.87	0.128
	Reserve HR	1	-	-	-	-	-	-
	Training volume							
	By week	17	0.005	0.003 - 0.007	<0.001	74%	0.84	<0.001

N = number of observations; VO_2 = Oxygen uptake; V_E/VCO_2 minute ventilation / carbon dioxide production; HR = Heart rate.

Table 4 | Aerobic exercise associations with mortality and hospitalizations.

Outcomes	Sample (total)	Fixed effects RR (95%CI)	Random effects RR (95%CI)
All-cause mortality	2559	0.93 (0.78-1.10)	0.92 (0.75-1.12)
Cardiac mortality	2548	0.84 (0.68-1.03)	0.60 (0.32-1.15)
All-cause hospitalization	2454	0.94 (0.86-1.02)	0.57 (0.19-1.77)
Cardiac hospitalization	2504	0.93 (0.85-1.02)	0.80 (0.41-1.59)
Hospitalization due heart failure	2598	0.83 (0.71-0.97)	0.76 (0.54-1.06)

RR = relative risk

Figures legend

Figure 1 | Systematic protocol of review process.

Figure 2 | Systematic search and screening process of randomised controlled trials.

Figure 3 | Association of aerobic exercise with peak oxygen uptake during the follow-up. Forest plot demonstrating the study-specific and weighted mean difference (WMD) effects in heart failure patients. 95%CI = 95% of confidence intervals.

Figure 4 | Association of aerobic exercise with minute ventilation / carbon dioxide production during the follow-up. Forest plot demonstrating the study-specific and weighted mean difference (WMD) effects in heart failure patients. 95%CI = 95% of confidence intervals.

Figure 5 | Association of aerobic exercise with maximal heart rate during the follow-up. Forest plot demonstrating the study-specific and weighted mean difference (WMD) effects in heart failure patients. 95%CI = 95% of confidence intervals.

Figure 6 | Association of aerobic exercise with first ventilatory threshold during the follow-up. Forest plot demonstrating the study-specific and weighted mean difference (WMD) effects in heart failure patients. 95%CI = 95% of confidence intervals.

Figure 7 | Sensitivity analyses of subjects and study characteristics with peak oxygen uptake and minute ventilation / carbon dioxide production. Subgroups were chosen a priori. WMD = weighted mean difference; 95%CI = 95% of confidence intervals.

Figure 8 | Sensitivity analyses of subjects and study characteristics with maximal heart rate and first ventilatory threshold. Subgroups were chosen a priori. WMD = weighted mean difference; 95%CI = 95% confidence intervals.

Figure 9 | Risk of bias assessment adapted from Cochrane Tool.

Figure 10 | Funnel plots of the association of aerobic exercise with exercise related outcomes.

Figure 1 |

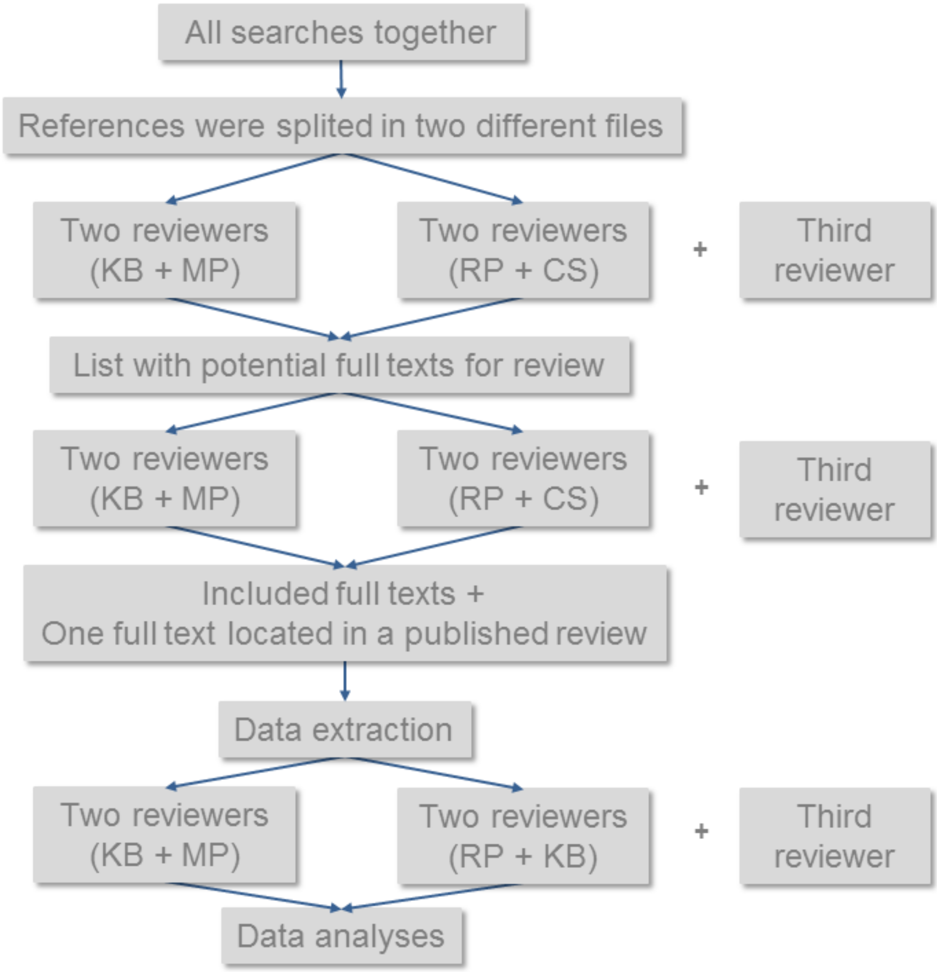
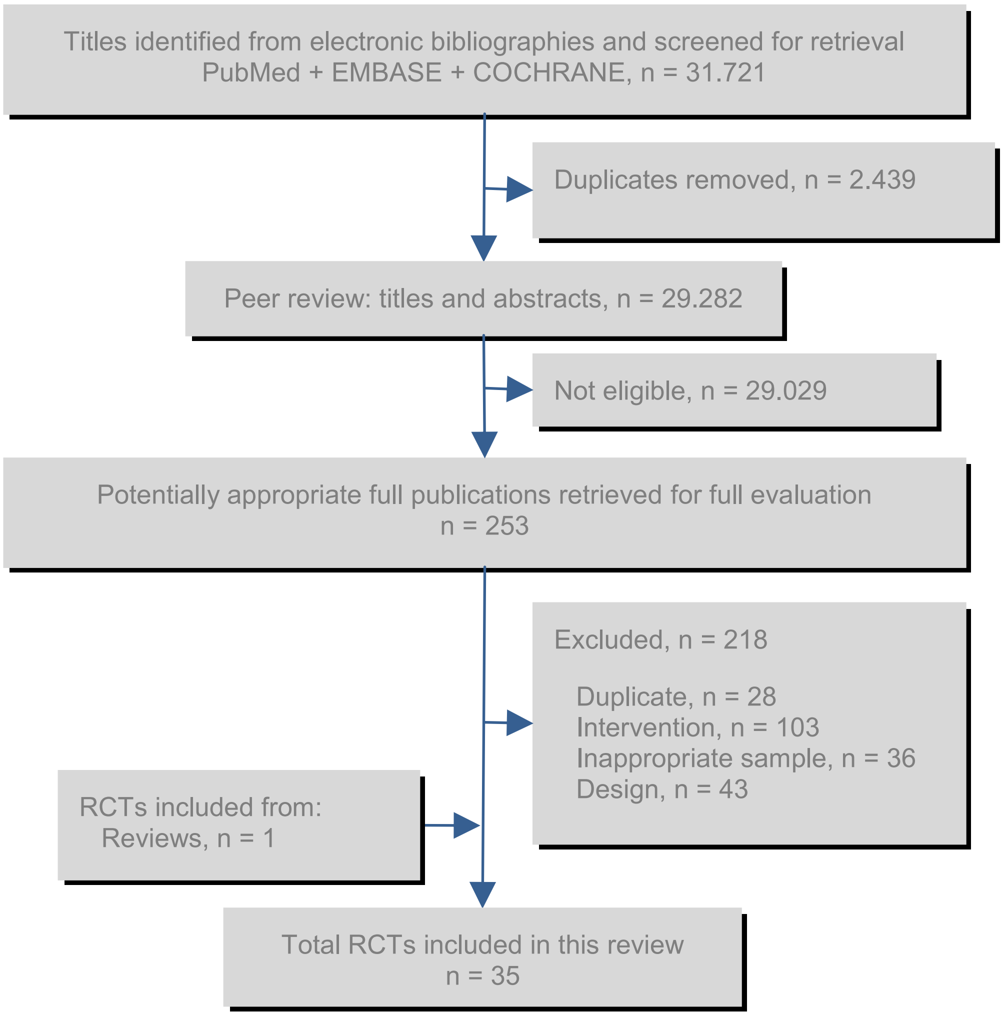

All searches together
References were splited in two different files
Two reviewers (KB + MP)
Two reviewers (RP + CS)
+
Third reviewer
List with potential full texts for review
Two reviewers (KB + MP)
Two reviewers (RP + CS)
+
Third reviewer
Included full texts +
One full text located in a published review
Data extraction
Two reviewers (KB + MP)
Two reviewers (RP + KB)
+
Third reviewer
Data analyses

Figure 2 |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PubMed + EMBASE + COCHRANE, n = 31.721
Duplicates removed, n = 2.439
Peer review: titles and abstracts, n = 29.282
Not eligible, n = 29.029
Potentially appropriate full publications retrieved for full evaluation
n = 253
Excluded, n = 218
Duplicate, n = 28
Intervention, n = 103
Inappropriate sample, n = 36
Design, n = 43
RCTs included from:
Reviews, n = 1
Total RCTs included in this review
n = 35

Figure 3 |

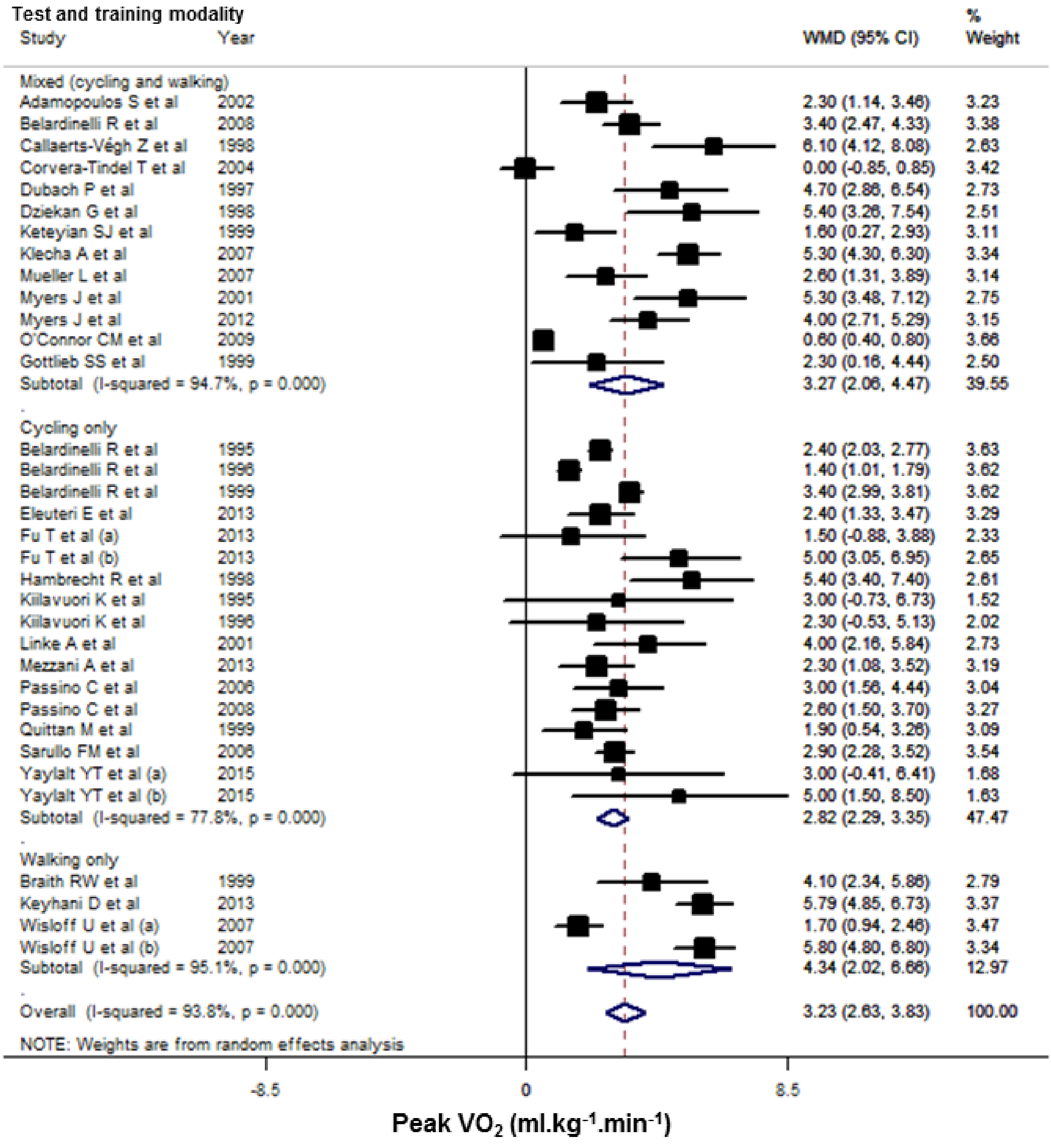
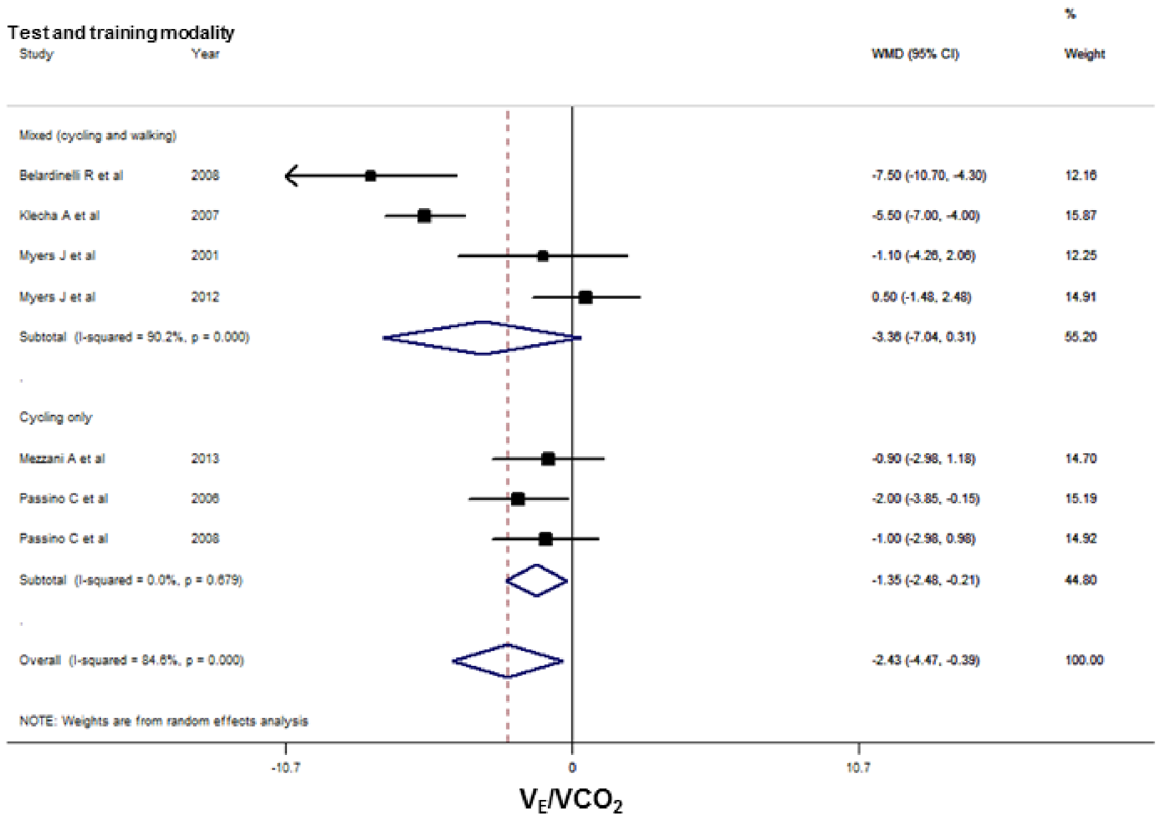

Test and training modality
Study Year
WMD (95% CI)
% Weight
Mixed (cycling and walking)
Adamopoulos S et al 2002 2.30 (1.14, 3.46) 3.23
Belardinelli R et al 2008 3.40 (2.47, 4.33) 3.38
Callaerts-Végh Z et al 1998 6.10 (4.12, 8.08) 2.63
Corvera-Tindel T et al 2004 0.00 (-0.85, 0.85) 3.42
Dubach P et al 1997 4.70 (2.86, 6.54) 2.73
Dziekan G et al 1998 5.40 (3.26, 7.54) 2.51
Keteyian SJ et al 1999 1.60 (0.27, 2.93) 3.11
Klecha A et al 2007 5.30 (4.30, 6.30) 3.34
Mueller L et al 2007 2.60 (1.31, 3.89) 3.14
Myers J et al 2001 5.30 (3.48, 7.12) 2.75
Myers J et al 2012 4.00 (2.71, 5.29) 3.15
O'Connor CM et al 2009 0.60 (0.40, 0.80) 3.66
Gottlieb SS et al 1999 2.30 (0.16, 4.44) 2.50
Subtotal (I-squared = 94.7%, p = 0.000) 3.27 (2.06, 4.47) 39.55
Cycling only
Belardinelli R et al 1995 2.40 (2.03, 2.77) 3.63
Belardinelli R et al 1996 1.40 (1.01, 1.79) 3.62
Belardinelli R et al 1999 3.40 (2.99, 3.81) 3.62
Eleuteri E et al 2013 2.40 (1.33, 3.47) 3.29
Fu T et al (a) 2013 1.50 (-0.88, 3.88) 2.33
Fu T et al (b) 2013 5.00 (3.05, 6.95) 2.65
Hambrecht R et al 1998 5.40 (3.40, 7.40) 2.61
Kiilavuori K et al 1995 3.00 (-0.73, 6.73) 1.52
Kiilavuori K et al 1996 2.30 (-0.53, 5.13) 2.02
Linke A et al 2001 4.00 (2.16, 5.84) 2.73
Mezzani A et al 2013 2.30 (1.08, 3.52) 3.19
Passino C et al 2006 3.00 (1.56, 4.44) 3.04
Passino C et al 2008 2.60 (1.50, 3.70) 3.27
Quittan M et al 1999 1.90 (0.54, 3.26) 3.09
Sarullo FM et al 2006 2.90 (2.28, 3.52) 3.54
Yaylalt YT et al (a) 2015 3.00 (-0.41, 6.41) 1.68
Yaylalt YT et al (b) 2015 5.00 (1.50, 8.50) 1.63
Subtotal (I-squared = 77.8%, p = 0.000) 2.82 (2.29, 3.35) 47.47
Walking only
Braith RW et al 1999 4.10 (2.34, 5.86) 2.79
Keyhani D et al 2013 5.79 (4.85, 6.73) 3.37
Wisloff U et al (a) 2007 1.70 (0.94, 2.46) 3.47
Wisloff U et al (b) 2007 5.80 (4.80, 6.80) 3.34
Subtotal (I-squared = 95.1%, p = 0.000) 4.34 (2.02, 6.66) 12.97
Overall (I-squared = 93.8%, p = 0.000) 3.23 (2.63, 3.83) 100.00
NOTE: Weights are from random effects analysis
-8.5
0
8.5
Peak VO2 (ml.kg-1.min-1)

Figure 4 |



Test and training modality
Study
Year
WMD (95% CI)
%
Weight
Mixed (cycling and walking)
Belardinelli R et al 2008 -7.50 (-10.70, -4.30) 12.16
Klecha A et al 2007 -5.50 (-7.00, -4.00) 15.87
Myers J et al 2001 -1.10 (-4.26, 2.06) 12.25
Myers J et al 2012 0.50 (-1.48, 2.48) 14.91
Subtotal (I-squared = 90.2%, p = 0.000) -3.36 (-7.04, 0.31) 55.20
Cycling only
Mezzani A et al 2013 -0.90 (-2.98, 1.18) 14.70
Passino C et al 2006 -2.00 (-3.85, -0.15) 15.19
Passino C et al 2008 -1.00 (-2.98, 0.98) 14.92
Subtotal (I-squared = 0.0%, p = 0.679) -1.35 (-2.48, -0.21) 44.80
Overall (I-squared = 84.6%, p = 0.000) -2.43 (-4.47, -0.39) 100.00
NOTE: Weights are from random effects analysis
-10.7
0
10.7
V_E/VCO_2

Figure 5 |

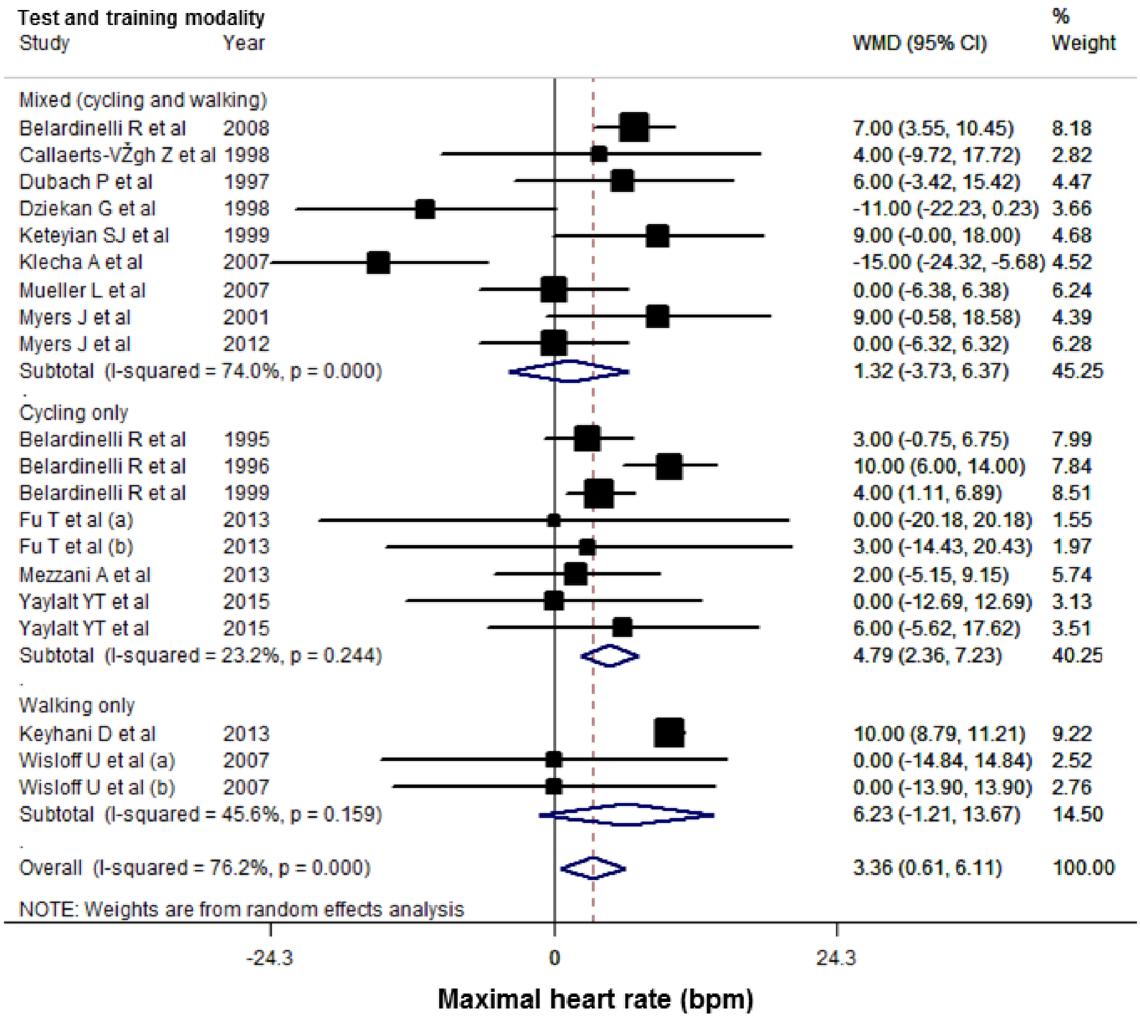

Test and training modality
Study Year
WMD (95% CI)
% Weight
Mixed (cycling and walking)
Belardinelli R et al 2008 7.00 (3.55, 10.45) 8.18
Callaerts-VŽgh Z et al 1998 4.00 (-9.72, 17.72) 2.82
Dubach P et al 1997 6.00 (-3.42, 15.42) 4.47
Dziekan G et al 1998 -11.00 (-22.23, 0.23) 3.66
Keteyian SJ et al 1999 9.00 (-0.00, 18.00) 4.68
Klecha A et al 2007 -15.00 (-24.32, -5.68) 4.52
Mueller L et al 2007 0.00 (-6.38, 6.38) 6.24
Myers J et al 2001 9.00 (-0.58, 18.58) 4.39
Myers J et al 2012 0.00 (-6.32, 6.32) 6.28
Subtotal (I-squared = 74.0%, p = 0.000) 1.32 (-3.73, 6.37) 45.25
Cycling only
Belardinelli R et al 1995 3.00 (-0.75, 6.75) 7.99
Belardinelli R et al 1996 10.00 (6.00, 14.00) 7.84
Belardinelli R et al 1999 4.00 (1.11, 6.89) 8.51
Fu T et al (a) 2013 0.00 (-20.18, 20.18) 1.55
Fu T et al (b) 2013 3.00 (-14.43, 20.43) 1.97
Mezzani A et al 2013 2.00 (-5.15, 9.15) 5.74
Yaylalt YT et al 2015 0.00 (-12.69, 12.69) 3.13
Yaylalt YT et al 2015 6.00 (-5.62, 17.62) 3.51
Subtotal (I-squared = 23.2%, p = 0.244) 4.79 (2.36, 7.23) 40.25
Walking only
Keyhani D et al 2013 10.00 (8.79, 11.21) 9.22
Wisloff U et al (a) 2007 0.00 (-14.84, 14.84) 2.52
Wisloff U et al (b) 2007 0.00 (-13.90, 13.90) 2.76
Subtotal (I-squared = 45.6%, p = 0.159) 6.23 (-1.21, 13.67) 14.50
Overall (I-squared = 76.2%, p = 0.000) 3.36 (0.61, 6.11) 100.00
NOTE: Weights are from random effects analysis
-24.3
0
24.3
Maximal heart rate (bpm)

Figure 6 |

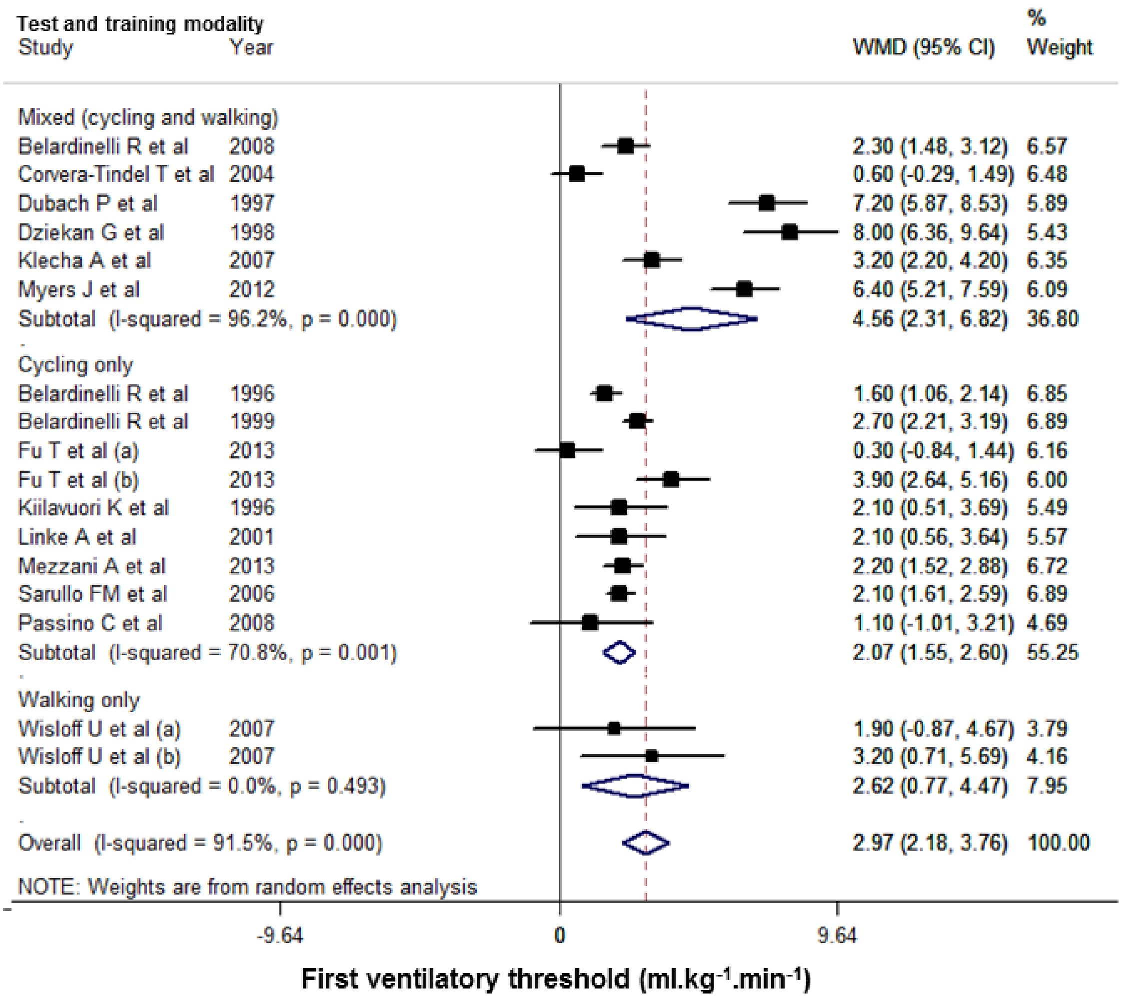
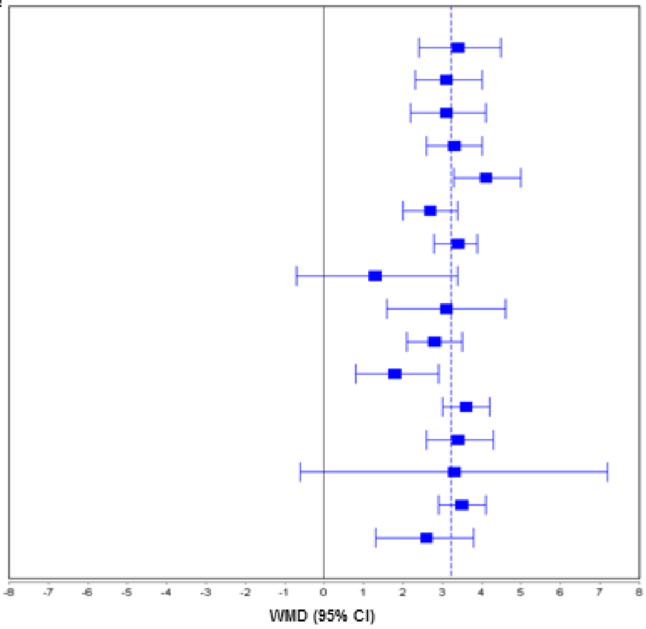

Test and training modality
Study Year
WMD (95% CI)
% Weight
Mixed (cycling and walking)
Belardinelli R et al 2008 2.30 (1.48, 3.12) 6.57
Corvera-Tindel T et al 2004 0.60 (-0.29, 1.49) 6.48
Dubach P et al 1997 7.20 (5.87, 8.53) 5.89
Dziekan G et al 1998 8.00 (6.36, 9.64) 5.43
Klecha A et al 2007 3.20 (2.20, 4.20) 6.35
Myers J et al 2012 6.40 (5.21, 7.59) 6.09
Subtotal (I-squared = 96.2%, p = 0.000) 4.56 (2.31, 6.82) 36.80
Cycling only
Belardinelli R et al 1996 1.60 (1.06, 2.14) 6.85
Belardinelli R et al 1999 2.70 (2.21, 3.19) 6.89
Fu T et al (a) 2013 0.30 (-0.84, 1.44) 6.16
Fu T et al (b) 2013 3.90 (2.64, 5.16) 6.00
Kiilavuori K et al 1996 2.10 (0.51, 3.69) 5.49
Linke A et al 2001 2.10 (0.56, 3.64) 5.57
Mezzani A et al 2013 2.20 (1.52, 2.88) 6.72
Sarullo FM et al 2006 2.10 (1.61, 2.59) 6.89
Passino C et al 2008 1.10 (-1.01, 3.21) 4.69
Subtotal (I-squared = 70.8%, p = 0.001) 2.07 (1.55, 2.60) 55.25
Walking only
Wisloff U et al (a) 2007 1.90 (-0.87, 4.67) 3.79
Wisloff U et al (b) 2007 3.20 (0.71, 5.69) 4.16
Subtotal (I-squared = 0.0%, p = 0.493) 2.62 (0.77, 4.47) 7.95
Overall (I-squared = 91.5%, p = 0.000) 2.97 (2.18, 3.76) 100.00
NOTE: Weights are from random effects analysis
-9.64
0
9.64
First ventilatory threshold (ml.kg-1.min-1)

Figure 7 |

Peak VO_2 ($ml.kg^{-1}.min^{-1}$)

Stratified analyses		Studies	WMD (95% CI)	I^2	p for I^2
Sex	> 90% men	14.0	3.4 (2.4-4.5)	85.0	<0.01
	≤ 90% men	15.0	3.1 (2.3-4.0)	96.0	<0.01
Age	> 55 years	17.0	3.1 (2.2-4.1)	96.0	<0.01
	≤ 55 years	14.0	3.3 (2.6-4.0)	84.0	<0.01
Ejection fraction	> 30%	10.0	4.1 (3.3-5.0)	72.0	<0.01
	≤ 30%	18.0	2.7 (2.0-3.4)	95.0	<0.01
NYHA IV	Not included	22.0	3.4 (2.8-3.9)	85.0	<0.01
	Included	3.0	1.3 (-0.7-3.4)	99.0	<0.01
Beta blockers	>75% using	7.0	3.1 (1.6-4.6)	96.0	<0.01
	≤ 75% using	14.0	2.8 (2.1-3.5)	75.0	<0.01
Intention to treat	Yes	6.0	1.8 (0.8-2.9)	95.0	<0.01
	No or unclear	25.0	3.6 (3.0-4.2)	88.0	<0.01
Intensity control	Yes	18.0	3.4 (2.6-4.3)	96.0	<0.01
	No	2.0	3.3 (-0.6-7.2)	92.0	<0.01
Supervision	Yes	20.0	3.5 (2.9-4.1)	86.0	<0.01
	No or both	9.0	2.5 (1.4-3.6)	95.0	<0.01



V_E/VCO_2

Stratified analyses		Studies	WMD (95% CI)	I^2	p for I^2
Sex	> 90% men	3.0	-0.3 (-1.6-1.0)	0.0	0.55
	≤ 90% men	4.0	-3.8 (-6.5- -1.2)	86.0	<0.01
Age	> 55 years	5.0	-3.2 (-5.6- -0.9)	85.0	<0.01
	≤ 55 years	2.0	0.05 (-1.6- 1.7)	0.0	0.4
Ejection fraction	> 30%	5.0	-2.0 (-4.2- 0.2)	78.0	<0.01
	≤ 30%	2.0	-3.3 (-7.8- 1.2)	92.0	<0.01
NYHA IV	Not included	6.0	-2.7 (-5.0- -0.4)	86.0	<0.01
Beta blockers	>75% using	3.0	-4.5 (-8.1- -0.9)	88.0	<0.01
	≤ 75% using	4.0	-0.9 (-2.0- 0.2)	9.0	0.35
Intention to treat	Yes	2.0	-4.1 (-10.5-2.4)	91.0	<0.01
	No or unclear	5.0	-1.9 (-4.2-0.4)	85.0	<0.01
Intensity control	Yes	6.0	-2.9 (-5.0--0.8)	82.0	<0.01
Supervision	Yes	3.0	-2.6 (-7.3-2.1)	89.0	<0.01
	No or both	3.0	-1.3 (-2.5- -0.2)	0.0	0.68

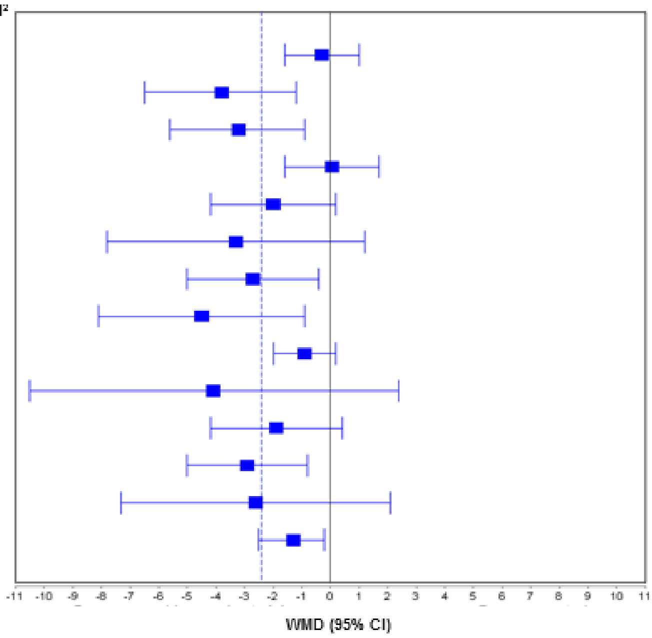
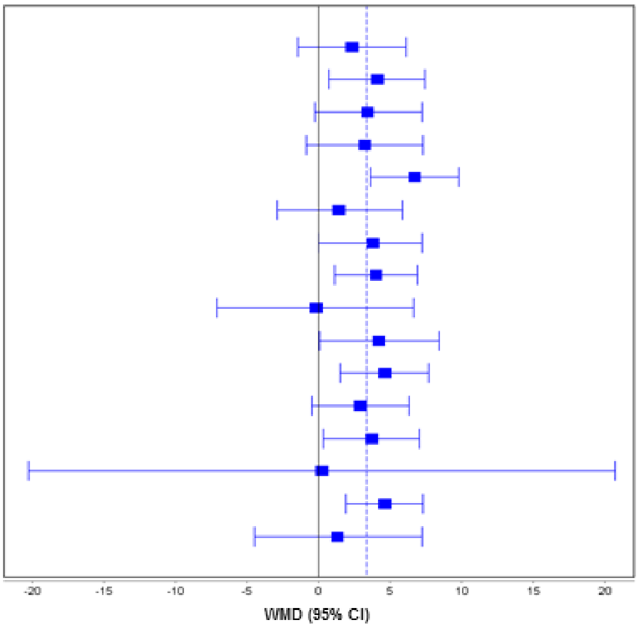


Figure 8 |

Maximal heart rate (bpm)

Stratified analyses		Studies	WMD (95% CI)	I^2	p for I^2
Sex	> 90% men	8.0	2.3 (-1.5 - 6.1)	37.0	0.14
	≤ 90% men	9.0	4.1 (0.7-7.4)	80.0	<0.01
Age	> 55 years	9.0	3.4 (-0.3 - 7.2)	78.0	<0.01
	≤ 55 years	8.0	3.2 (-0.9-7.3)	65.0	<0.01
Ejection fraction	> 30%	8.0	6.7 (3.6-9.8)	49.0	0.06
	≤ 30%	7.0	1.4 (-2.9-5.8)	76.0	<0.01
NYHA IV	Not included	11.0	3.8 (-0.01 - 7.2)	80.0	<0.01
	Included	1.0	4.0 (1.1-6.9)	-	-
Beta blockers	>75% using	6.0	-0.2 (-7.1-6.6)	70.0	<0.01
	≤ 75% using	3.0	4.2 (0.01-8.4)	6.0	0.37
Intention to treat	Yes	3.0	4.6 (1.5-7.7)	34.0	0.22
	No or unclear	14.0	2.9 (-0.5-6.3)	77.0	<0.01
Intensity control	Yes	12.0	3.7 (0.3-7.0)	78.0	<0.01
	No	2.0	0.2 (-20.3-20.7)	92.0	<0.01
Supervision	Yes	13.0	4.6 (1.9-7.3)	73.0	<0.01
	No or both	2.0	1.3 (-4.5-7.2)	0.0	0.95



First ventilatory threshold (ml.kg^{-1}.min^{-1})

Stratified analyses		Studies	WMD (95% CI)	I^2	p for I^2
Sex	> 90% men	7.0	4.1 (2.0-6.2)	96.0	<0.01
	≤ 90% men	8.0	2.2 (1.7-2.8)	72.0	<0.01
Age	> 55 years	9.0	2.1 (1.5-2.8)	75.0	<0.01
	≤ 55 years	6.0	4.5 (2.6-6.4)	96.0	<0.01
Ejection fraction	> 30%	4.0	3.8 (1.0-6.6)	95.0	<0.01
	≤ 30%	11.0	2.5 (1.9-3.2)	85.0	<0.01
NYHA IV	Not included	10.0	3.0 (2.0-4.0)	92.0	<0.01
	Included	2.0	1.7 (-0.4-3.7)	94.0	<0.01
Beta blockers	>75% using	5.0	2.4 (1.5-3.2)	72.0	<0.01
	≤ 75% using	6.0	2.4 (0.9-4.0)	92.0	<0.01
Intention to treat	Yes	3.0	1.7 (0.7-2.7)	79.0	<0.01
	No or unclear	12.0	3.3 (2.3-4.2)	92.0	<0.01
Intensity control	Yes	8.0	2.8 (1.9-3.8)	87.0	<0.01
	No	2.0	4.7 (-1.5-11.0)	98.0	<0.01
Supervision	Yes	10.0	3.4 (2.4-4.5)	94.0	<0.01
	No or both	4.0	1.6 (0.6-2.6)	58.0	0.04

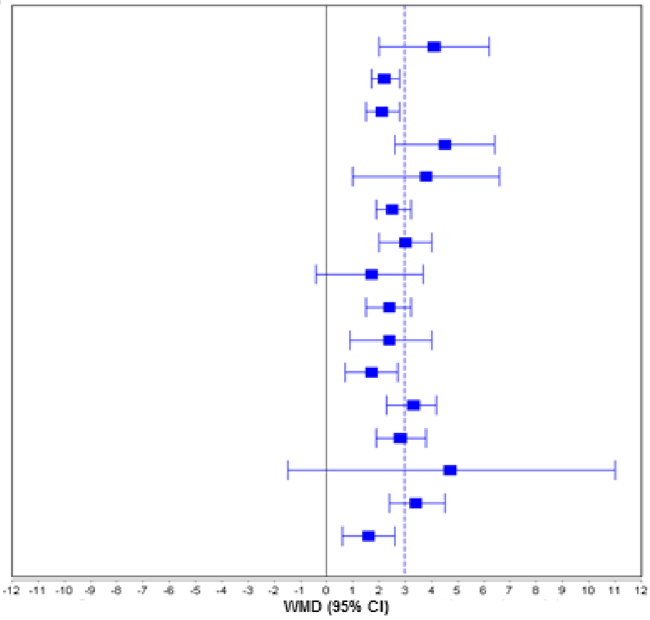


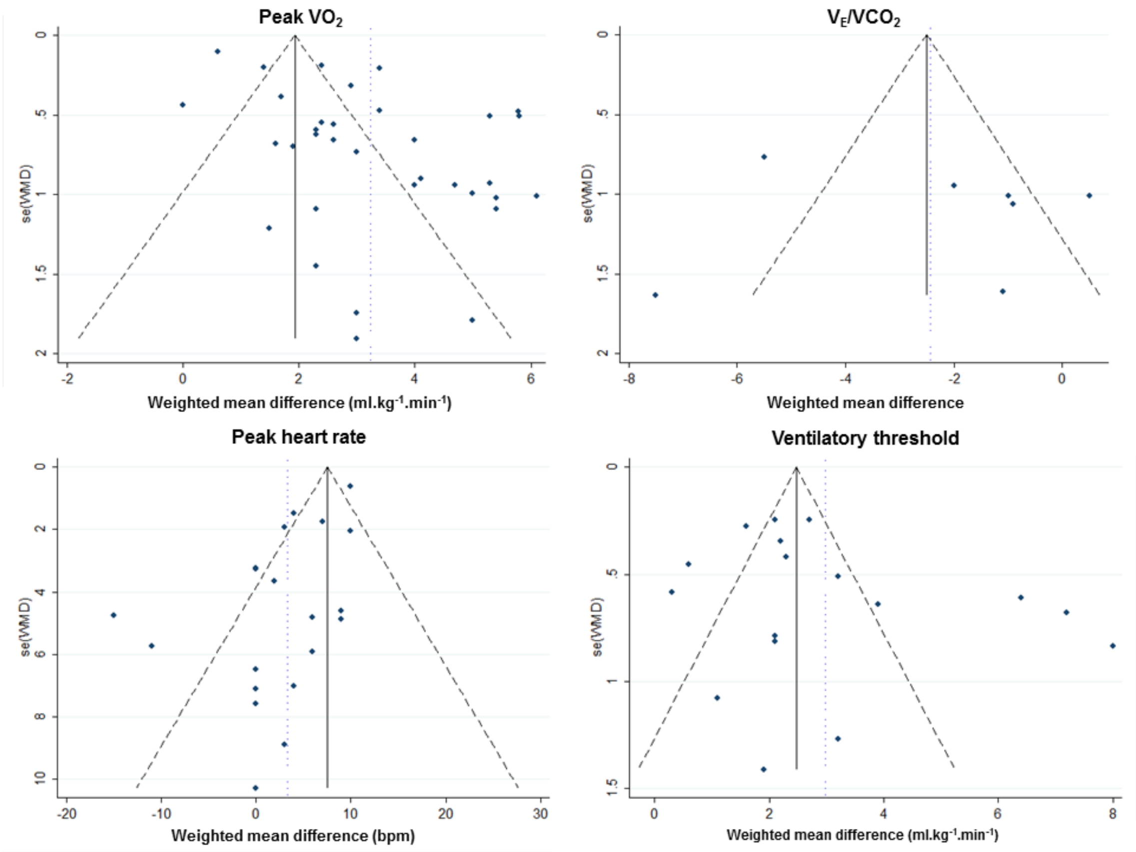
Figure 9 |

	Random sequence generation	Allocation concealment	Blinding of outcome assesment	Incomplete outcome data	Selective reporting	Sample size calculation
Adamopoulos S et al 2002	?	?	+	?	+	?
Belardinelli R et al 1995	+	?	?	+	+	?
Belardinelli R et al 1996	+	?	?	+	+	?
Belardinelli R et al 1999	?	?	?	+	+	?
Belardinelli R et al 2008	+	+	?	+	+	+
Belardinelli R et al 2012	?	?	+	-	+	+
Braith RW et al 1999	?	?	?	?	?	?
Callaerts-Végh Z et al 1998	?	?	?	+	?	?
Collins E et al 2004	?	?	+	+	+	+
Corvera-Tindel T et al 2004	?	?	+	-	+	+
Dehkordi AH 2015	+	?	?	?	+	+
Dubach P et al 1997	+	?	+	+	-	?
Dziekan G et al 1998	+	?	?	+	+	?
Eleuteri E et al 2013	?	?	?	+	?	?
Fu T et al 2013	?	?	?	?	+	?
Gottlieb SS et al 1999	?	?	?	-	+	?
Hambrecht R et al 1998	?	?	?	+	+	?
Keteyian SJ et al 1999	?	?	?	-	+	?
Keyhani D et al 2013	?	?	?	+	-	?
Kiilavuori K et al 1995	?	?	?	?	-	?
Kiilavuori K et al 1996	?	?	?	?	+	?
Klecha A et al 2007	?	?	-	+	+	?
Klocek M et al 2005	?	?	?	+	+	?
Linke A et al 2001	?	?	?	+	?	?
Mezzani A et al 2013	+	?	+	+	+	+
Mueller L et al 2007	?	?	?	+	+	?
Myers J et al 2001	?	?	?	+	+	?
Myers J et al 2012	+	?	?	+	+	?
O'Connor CM et al 2009	+	?	-	+	+	+
Passino C et al 2006	?	?	?	-	?	?
Passino C et al 2008	+	?	?	-	?	?
Quittan M et al 1999	+	?	?	+	?	?
Sarullo FM et al 2006	+	+	+	+	+	?
Wisloff U et al 2007	+	?	?	+	-	?
Yaylalt YT et al 2015	+	+	?	-	?	?

Key

+ Low risk of bias
- High risk of bias
? Unclear risk of bias

Figure 10 |



Peak VO2
se(WMD)
Weighted mean difference (ml.kg-1.min-1)
VE/VCO2
se(WMD)
Weighted mean difference
Peak heart rate
se(WMD)
Weighted mean difference (bpm)
Ventilatory threshold
se(WMD)
Weighted mean difference (ml.kg-1.min-1)

Supplementary material

S1 | References from the 35 articles included in this systematic review and meta-analysis.

Adamopoulos S, Parissis J, Karatzas D, Kroupis C, Georgiadis M, Karavolias G, Paraskevaidis J, Koniavitou K, Coats AJ, Kremastinos DT. Physical training modulates proinflammatory cytokines and the soluble Fas/soluble Fas ligand system in patients with chronic heart failure. J Am Coll Cardiol. 2002;39:653-63.

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Table S1 | Study contributions to individual outcomes.

First Author	Publication year	Peak VO_2	Maximal HR	V_E/VCO_2	1^{st} VT	All-cause mortality	Cardiac mortality	All-cause hospitalization	Cardiac hospitalization	Hospitalization due hart failure
Adamopoulos S	2002	✔								
Belardinelli R	1995	✔	✔			✔				
Belardinelli R	1996	✔	✔		✔					
Belardinelli R	1999	✔	✔		✔		✔			✔
Belardinelli R	2008	✔	✔	✔	✔					
Belardinelli R	2012					✔	✔	✔	✔	✔
Braith RW	1999	✔								
Callaerts-Végh Z	1998	✔	✔							
Collins E	2004									
Corvera-Tindel T	2004	✔			✔					
Dehkordi AH	2015									
Dubach P	1997	✔	✔		✔					
Dziekan G	1998	✔	✔		✔					
Eleuteri E	2013	✔								
Fu T	2013	✔	✔		✔					

Gottlieb SS	1999	✔								
Hambrecht R	1998	✔								
Keteyian SJ	1999	✔	✔							
Keyhani D	2013	✔	✔							
Kiilavuori K	1995	✔								
Kiilavuori K	1996	✔			✔					
Klecha A	2007	✔	✔	✔	✔					
Klocek M	2005									
Linke A	2001	✔			✔					
Mezzani A	2013	✔	✔	✔	✔					
Mueller L	2007	✔	✔			✔			✔	✔
Myers J	2001	✔	✔	✔						
Myers J	2012	✔	✔	✔	✔					
O'Connor CM	2009	✔				✔	✔	✔	✔	✔
Passino C	2006	✔		✔						
Passino C	2008	✔		✔	✔					
Quittan M	1999	✔								
Sarullo FM	2006	✔			✔					

Wisloff U	2007	✔	✔			✔
Yaylalt YT	2015	✔	✔			

VO_2 = Oxygen uptake; HR = Heart rate; V_E/VCO_2 minute ventilation / carbon dioxide production; VT = ventilatory threshold.

Capítulo V

5. Considerações finais

Os resultados do estudo indicaram que os benefícios do exercício no VO_2 pico foram independentes da idade, percentual de homens nas amostras, fração de ejeção, uso de beta-bloqueadores, modalidade de treinamento, supervisão da sessão e/ou modalidade do treinamento. Pacientes com NYHA I-III e protocolos que controlaram a intensidade foram associados com aumento do VO_2 pico. A intensidade alvo se associou positivamente com os aumentos em VO_2 pico, independente da idade, fração de ejeção e volume semanal de treino.

Os benefícios do exercício aeróbico no V_E/VCO_2 e na FC máxima foram observados apenas nos estudos que utilizaram exclusivamente cicloergômetro para o teste e treino. O percentual de homens e a idade da amostra, uso de beta-bloqueadores, controle da intensidade e supervisão do treinamento também influenciaram nos benefícios no V_E/VCO_2. Enquanto que para a FC máxima estudos com menor percentual de homens, FE mais elevada, menor uso de beta-bloqueadores, análise por intenção de tratar, controle da intensidade e supervisão do treinamento se associaram aos benefícios. Para o primeiro LV, todas as modalidades de teste e treino se associaram a resultados positivos, sendo esta melhora independente do sexo, idade, fração de ejeção, uso de beta-bloqueadores e supervisão do treinamento. Pacientes com NYHA I-III e submetidos a treinamento com controle de intensidade também apresentaram melhora do primeiro LV. A intensidade alvo do treinamento influenciou os ganhos no LV, independente da idade, fração de ejeção e volume semanal de treino.

Os achados apresentados trazem implicações quanto à escolha do programa de treinamento que será prescrito pelos profissionais que trabalham com insuficiência cardíaca, tanto em nível de pesquisa, quanto assistencial. Ademais, estas diferenças podem explicar parte da dificuldade existente para estabelecer uma concordância entre os efeitos apresentados pelos diferentes estudos, quando avaliados desfechos clínicos a médio e longo prazo.

APÊNDICE A - Fichas de leitura das revisões

Título do artigo

Exercise training for patients with heart failure: a systematic review of factors that improve mortality and morbidity

Primeiro autor

Neil Smart

Ano da publicação

2004

Objetivo

"To determine the efficacy of exercise training and its effects on outcomes in patients with heart failure."

Conclusão

“Exercise training is safe and effective in patients with heart failure. The risk of adverse events may be reduced, but further studies are required to determine whether there is any mortality benefit.”

Título do artigo

Exercise based rehabilitation for heart failure.

Primeiro autor

Rees

Ano da publicação

2004

Objetivo

"To determine the effectiveness of exercise based interventions compared with usual medical care on the mortality, morbidity, exercise capacity and health related quality of life, of patients with heart failure."

Conclusão

“Exercise training improves exercise capacity and quality of life in patients mild to moderate heart failure in the short term. There is currently no information regarding the effect of exercise training on clinical outcomes. The findings are based on small-scale trials in patients who are unrepresentative of the total population of patients with heart failure. Other groups (more severe patients, the elderly, women) may also benefit. Large-scale pragmatic trials of exercise training of longer duration, recruiting a wider spectrum of patients are needed to address these issues.”

Título do artigo

Exercise training meta-analysis of trials in patients with chronic heart failure (ExTraMATCH)

Primeiro autor

ExTraMATCH collaborative

Ano da publicação

2004

Objetivo

"To determine the effect of exercise training on survival in patients with heart failure due to left ventricular systolic dysfunction."

Conclusão

“Meta-analysis of randomised trials to date gives no evidence that properly supervised medical training programmes for patients with heart failure might be dangerous, and indeed there is clear evidence of an overall reduction in mortality.”

Título do artigo

Effects of exercise training on cardiac performance, exercise capacity and quality of life in patients with heart failure: a meta-analysis

Primeiro autor

Benno A. F. van Tol

Ano da publicação

2006

Objetivo

"To determine the effect of exercise training in patients with chronic heart failure on cardiac performance, exercise capacity and health-related quality of life."

Conclusão

“Exercise training has clinically important effects on exercise capacity and health-related quality of life, and may have small positive effects on cardiac performance during exercise.”

Título do artigo

A meta-analysis of the effect of exercise training on left ventricular remodeling in heart failure patients

Primeiro autor

Mark J. Haykowsky

Ano da publicação

2007

Objetivo

"... to determine the effect of exercise training and type of exercise on left ventricular remodeling in heart failure."

Conclusão

“Aerobic training reverses left ventricular remodeling in clinically stable individuals with heart failure. This benefit was not confirmed with combined aerobic and strength training.”

Título do artigo

Effect of outpatient exercise training programmes in patients with chronic heart failure: a systematic review.

Primeiro autor

Simon van der Meer

Ano da publicação

2012

Objetivo

“Therefore, this systematic review studies the effects of outpatient exercise training programmes compared with usual care on exercise capacity, exercise performance, quality of life, and safety in patients with chronic heart failure.”

Conclusão

“This meta-analysis illustrates the efficacy and safety of outpatient training programmes for patients with chronic heart failure.”

Título do artigo

Effects of exercise training on left ventricular remodeling in heart failure patients: an update meta-analysis of randomized controlled trials

Primeiro autor

Y M. Chen

Ano da publicação

2013

Objetivo

"... to determine whether exercise training reversed left ventricular remodeling in heart failure patients."

Conclusão

“Aerobic exercise training, especially long-term duration (>= 6 months) reverses left ventricular remodeling in clinally stable patients with heart failure. Strength training (alone or plus aerobic training) did not improve or worsen ventricular remodeling.”

Título do artigo

Is exercise training beneficial fo heart failure patients taking β-adrenegic blockers? A systematic review and meta-analysis

Primeiro autor

Hasbullah Ismail

Ano da publicação

2013

Objetivo

"... to estabilish whether β-blockers attenuated physical training adaptations in heart failure patients."

Conclusão

"Our analysis demonstrated that β-adrenergic blocker therapy did not reduce exercise capacity of exercise training adaptations and quality of life in heart failure patients."

Título do artigo

Aerobic exercise effect on prognostic markers for systolic heart failure patients: a systematic review and meta-analysis

Primeiro autor

Gerson Cipriano Jr

Ano da publicação

2013

Objetivo

"The primary aim of the proposed study is to determine the effect of aerobic exercise training on minute ventilation/carbon dioxide production slope and NTproBNP."

Conclusão

"Aerobic exercise may be effective at improving NTproBNP and the VE/VCO2 slope in systolic HF patients, but these effects are limited to a specific HF population meeting specific inclusion criterion in a limited number of studies. Future randomized controlled studies including diastolic and HF overleap with pulmonary diseases are needed to better understand the exact influence of AEX."

Título do artigo

Meta-analysis of aerobic interval training on exercise capacity and systolic function in patients with heart failure and reduced ejection fractions

Primeiro autor

Mark J. Hayakowsky

Ano da publicação

2013

Objetivo

"... to examine the effects of aerobic interval training compared with those moderate-intensity continuous aerobic exercise training on these outcomes."

Conclusão

"In conclusion, in clinically stable patients with heart failure with reduced ejection fraction, aerobic interval training is more effective than moderate-intensity continuous aerobic training for improvind peak peak oxygen uptake but not left ventricular ejection fraction at rest."

Título do artigo

Clinical outcomes and cardiovascular responses to different exercise training intensities in patients with heart failure

Primeiro autor

Hashbullah Ismail

Ano da publicação

2013

Objetivo

“... to establish wheather aerobic exercise training produces different effect sizes for fitness, adherence, event rates, mortality rates, and hospitalization rates in patients with heart failure.”

Conclusão

“As exercise training intensity rises, so may the magnitude of improvement in cardiorespiratory fitness, accompanied by lower study withdrawal in exercising patients. Total exercise time may be a confounder.”

Título do artigo

Exercise-based cardiac rehabilitation in patients with heart failure: a meta-analysis of randomised controlled trials between 1999 and 2013

Primeiro autor

Christian Lewinter

Ano da publicação

2014

Objetivo

“The presente study adress this gap and also updates the meta-analysis to include outcomes of mortality, hospital admission and standardised exercise capacity in patients with heart failure attending exercise-based cardiac rehabilitation.”

Conclusão

“Exercise-based cardiac rehabilitation in patients is associated with significant improvements in exercise capacity and hospital admission over a minimum of six months follow-up, but not in all-cause mortality.”

Título do artigo

Exercise-based rehabilitation for heart failure (Review)

Primeiro autor

Rod S Taylor

Ano da publicação

2014

Objetivo

“To determine the effectiveness of exercise-based rehabilitation on the mortality, hospitalization admissions mobidity and health-related quality of life for people with heart failure.

Conclusão

“This updated Cochrane review supports the conclusions of the previous version of this review that, compared with no exercise control, exercise-based rehabilitation does not increase or decrease the risk of all-cause mortality in the short term (up to 12-months' follow-up) but reduces the risk of hospital admissions and confers important improvements in health-related quality of life. This update provides further evidence that exercise training may reduce mortality in the longer term and that the benefits of exercise training on appear to be consistent across participant characteristics including age, gender and HF severity. Further randomised controlled trials are needed to confirm the small body of evidence seen in this review for the benefit of exercise in HFPEF and when exercise rehabilitation is exclusively delivered in a home-based setting.”

Título do artigo

Exercise-based rehabilitation for heart failure: systematic review and meta-analysis

Primeiro autor

Viral A Sagar

Ano da publicação

2015

Objetivo

"To update the Cochrane systematics review of exercise-based cardiac rehabilitation for heart failure."

Conclusão

“This updated Cochrane review shows that improvements in hospitalisation and health-related quality of life with exercise-based CR appear to be consistent across patients regardless of CR programme characteristics and may reduce mortality in the longer term. An individual participant data meta-analysis is needed to provide confirmatory evidence of the importance of patient subgroup and programme level characteristics (eg, exercise dose) on outcome.”

Título do artigo

The influence of training characteristics on the effect of aerobic exercise training in patients with chronic heart failure: a meta-regression analysis.

Primeiro autor

Ton Vromen

Ano da publicação

2016

Objetivo

"… to determine a ranking of the individual effect of training characteristics on the improvement in exercise capacity of an aerobic exercise training program in chronic heart failure patients."

Conclusão

“These results suggest that the design of a training program requires high total energy expenditure as a main goal. Increases in training frequency and session duration appear to yield the largest improvement in exercise capacity.”