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TESE DE DOUTORADO

MÚSCULOS INSPIRATÓRIOS E CONTROLE REFLEXO DA CIRCULAÇÃO E DA VENTILAÇÃO

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Dedico essa tese a minha família fonte de amor e inspiração.

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LISTA DE ABREVIATURAS

ICC	insuficiência cardíaca crônica
CO_2	gás carbônico
$\dot{V}_E/\dot{V}_{CO2}$ slope	relação da inclinação entre a ventilação e a produção de gás carbônico
DPOC	doença pulmonar obstrutiva crônica
PO_2	pressão parcial de oxigênio
PCO_2	pressão parcial de gás carbônico
pH	concentração hidrogênica
$\dot{V}O_2$	consumo de oxigênio
$\dot{V}O_{2máx}$	consumo máximo de oxigênio
$\dot{V}O_{2pico}$	consumo de oxigênio de pico
$\dot{V}O_{2peak}$	peak oxygen uptake
PImax	maximal inspiratory pressure
TI/TTot	razão entre o tempo inspiratório e duração total do ciclo respiratório
$SatO_2$	saturação de oxigênio
PET_{CO2}	pressão de CO_2 ao término da expiração
PI UAC	inspiratory pressure expressed as area under a curve
IMW	inspiratory muscle weakness
CHF	chronic heart failure
ACE	angiotensin-converting enzyme

RESUMO

Introdução: O treinamento da musculatura inspiratória pode atenuar o metaborreflexo inspiratório em indivíduos saudáveis e normalizar as respostas ventilatórias anormais ao exercício associadas com elevação do quimiorreflexo periférico em pacientes com insuficiência cardíaca crônica (ICC) e fraqueza muscular inspiratória.

Objetivos: Testar a hipótese que indivíduos treinados aerobicamente apresentam atenuação do metaborreflexo inspiratório. Testar a hipótese que pacientes com ICC e fraqueza muscular inspiratória apresentam aumento da resposta quimiorreflexa periférica comparado aos pacientes com força muscular inspiratória preservada.

Metodologia: O metaborreflexo inspiratório foi estudado em 9 indivíduos treinados (23 ± 0,7 anos) e 9 sedentários saudáveis (24 ± 0,7 anos) através da indução de trabalho muscular inspiratório fatigante (resistência inspiratória de 60% da pressão inspiratória máxima [PImáx]. O quimiorreflexo periférico foi estudado através do teste de uma inalação única de 13% CO_2 em 19 pacientes com ICC: 9 com fraqueza muscular inspiratória (PImáx < 70% do predito para o sexo e idade) e 10 com força muscular inspiratória preservada.

Resultados: O trabalho muscular inspiratório fatigante aumentou a pressão arterial média similarmente nos indivíduos treinados e nos sedentários. O fluxo sanguíneo poplíteo foi reduzido nos indivíduos sedentários, mas não foi alterado nos treinados. A resistência vascular periférica foi aumentada nos sedentários (de 559 ± 35 para 757 ± 56 unidades) mas não foi alterada nos

indivíduos treinados (de 528 ± 69 para 558 ± 64 unidades). Os pacientes com fraqueza muscular inspiratória apresentaram maior resposta quimiorreflexa periférica (0,11 ± 0,03 $l.min^{-1}.Torr^{-1}$) comparado aos pacientes com força muscular inspiratória preservada (0,07 ± 0,03 $l.min^{-1}.Torr^{-1}$, p = 0,02). A resposta quimiorreflexa periférica foi inversamente correlacionada com a PImáx (r = - 0,57; p = 0,01).

Conclusão: Indivíduos saudáveis treinados aerobicamente apresentam atenuação do metaborreflexo muscular inspiratório. A fraqueza muscular inspiratória está associada à exacerbação do quimiorreflexo periférico em pacientes com ICC.

INTRODUÇÃO

O condicionamento dos músculos respiratórios melhora a capacidade funcional e as respostas ventilatórias ao exercício progressivo em indivíduos que apresentam redução da força e da resistência muscular inspiratória associada à ICC (1). Atualmente, sabe-se que o aumento do trabalho muscular inspiratório limita o desempenho físico tanto nos pacientes com ICC quanto nos indivíduos saudáveis (2,3,4). Há evidências de que essa limitação no desempenho é mediada por um mecânismo denominado “metaboreflexo inspiratório”, no qual fibras nervosas quimiosensíveis são sensibilizadas pelo acúmulo de metabólitos durante o exercício muscular fatigante (5) promovendo aumento da atividade simpática (6) e vasoconstrição periférica (7,8). O metaborreflexo inspiratório pode ser atenuado pelo treinamento muscular inspiratório, tanto nos pacientes com insuficiência cardíaca (9) quanto nos indivíduos saudáveis (10,11). Apesar do exercício físico regular melhorar a resistência muscular inspiratória (12), ainda não é conhecido se o treinamento aeróbico modifica o metaborreflexo inspiratório.

Da mesma forma que o condicionamento da musculatura respiratória pode melhorar o desempenho físico, o descondicionamento dessa musculatura poderia estar associado com reduções no desempenho físico. Os pacientes com ICC frequentemente apresentam fraqueza muscular inspiratória (1,13,14) e respostas ventilatórias anormais ao exercício progressivo, como inclinação da relação entre a ventilação e a produção de CO_2 ($\dot{V}_E/\dot{V}_{CO2}$) aumentada e ventilação periódica (15). Essas respostas anormais ao exercício parecem

relacionadas a atividade quimiorreflexa aumentada (16,17). O treinamento muscular inspiratório melhora as respostas ventilatórias ao exercício progressivo, reduzindo a inclinação $\dot{V}_E/\dot{V}_{CO2}$ e a ventilação oscilatória (1). Esse efeito do treinamento muscular inspiratório sobre as respostas ventilatórias ao exercício sugere que a força muscular inspiratória possa estar relacionada com o quimiorreflexo.

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OBJETIVOS

1. Testar a hipótese de que o metaborreflexo inspiratório esteja atenuado em invidíduos aerobicamente treinados.
2. Testar a hipótese de que a fraqueza muscular inspiratória esteja associada com quimiorreflexo periférico aumentado em pacientes com ICC.

REVISÃO DA LITERATURA

1. Introdução

Os mecanismos envolvidos nas respostas hemodinâmicas e ventilatórias ao exerçício são estudados intensamente há vários anos (1). No entanto, apenas na última década foi evidênciado que a musculatura respiratória contribui importantemente com a redistribuição do fluxo sanguíneo (1) e com as respostas ventilatórias ao exercício progressivo (2). Os músculos respiratórios são amplamente inervados por fibras nervosas quimiosensíveis, denominadas metaborreceptores, as quais respondem ao acúmulo de metabólitos produzidos durante exercício intenso associado com fadiga muscular inspiratória (3). A ativação dos metaborreceptores da musculatura inspiratória aumenta os níveis de noradrenalina (4), eleva a atividade nervosa simpática muscular (5) e induz vasoconstrição periférica (6,7,8) reduzindo o fluxo sanguíneo para a musculatura esquelética inativa (6,7), bem como para a musculatura esquelética ativa (4). Consequentemente, a restrição do fluxo sanguíneo para a musculatura esquelética ativa pode prejudicar o desempenho físico durante o exercício (9). Dessa forma, o metaborreflexo inspiratório pode apresentar efeitos relevantes para indivíduos envolvidos em competições esportivas (10) e para aqueles que apresentam redução do desempenho muscular inspiratório relacionado com a ICC (8,11) e com a doença pulmonar obstrutiva crônica (DPOC) (12).

As respostas ventilatórias ao exercício são moduladas pelo quimiorreflexo, mas também podem ser influenciadas pelos metaborreceptores

(13). Os quimiorreceptores, sensibilizados pelas variações na pressão parcial de oxigênio (PO_2), pressão parcial de gás carbônico (PCO_2) e pela concentração hidrogênica (pH) do sangue arterial (14), aumentam o trabalho muscular inspiratório para suprir a demanda ventilatória. No entanto, pouco é conhecido sobre a relação entre os músculos respiratórios e o controle quimiorreflexo. Sabe-se que a fraqueza muscular inspiratória está relacionada com respostas ventilatórias anormais ao exercício progressivo, como a ventilação oscilatória e o aumento da inclinação $\dot{V}_E/\dot{V}_{CO2}$ em pacientes com ICC (2). Essas respostas anormais ao exercício parecem derivar da exarcebação do quimiorreflexo e/ou do metaborreflexo (13).

A presente revisão tem como objetivos: (1) descrever o metaborreflexo inspiratório, seu papel na limitação do desempenho físico e os efeitos de intervenções que poderiam atenuar o metaborreflexo inspiratório; (2) descrever o quimiorreflexo, seus efeitos sobre capacidade funcional e controle da ventilação durante o exercício e explorar a relação entre musculatura inspiratória e quimiorreflexo na ICC. Finalmente, identificaremos as lacunas do conhecimento sobre os temas aqui referenciados.

2. **Redistribuição da circulação durante o exercício**

Durante o exercício, o débito cardíaco aumenta linearmente com o aumento do consumo de O_2 ($\dot{V}O_2$). Ao mesmo tempo, o fluxo sanguíneo é redistribuído das áreas inativas para os músculos esqueléticos ativos e miocárdio. A contração muscular esquelética ativa receptores sensíveis a

deformação mecânica da unidade musculotendinosa (mecanorreceptores) e receptores sensíveis ao acúmulo de metabólitos (metaborreceptores). A ativação desses receptores, constituídos por fibras mielínicas (grupo III) ou amielínicas (grupo IV), resulta no aumento dos disparos simpáticos para o leito vascular sistêmico promovendo vasoconstrição dos músculos esqueléticos inativos e das regiões esplâncnica, renal e mesentérica. Já nos músculos ativos ocorre vasodilatação mediada pelo acúmulo de metabólitos. Dessa forma, o débito cardíaco é redistribuído dos músculos inativos para aqueles com demanda metabólica aumentada, um efeito resultante do metaborreflexo (1).

A ativação do metaborreflexo pela contração dos músculos esqueléticos é amplamente conhecida. Entretanto, apenas na última década foi descoberto que o metaborreflexo também pode ser ativado pelo trabalho dos músculos respiratórios (5,6,7,15) o que acarreta importantes repercussões para o desempenho físico.

2.1 Metaborreflexo inspiratório

O grupo de pesquisa do Prof. Jerome Dempsey descreveu o "metaborreflexo inspiratório" a partir de uma série de estudos (4,5,6,7,16,17). Inicialmente, foi demonstrado que o exercício físico (intensidade > 85% do consumo máximo de oxigênio [$\dot{V}O_{2máx}$]) induz fadiga muscular diafragmática (18) até mesmo em atletas de elite (19). Em seguida, foi descoberto que o aumento do trabalho muscular inspiratório (via resistência inspiratória) eleva os

níveis de noradrenalina, reduzindo o fluxo sanguíneo da perna durante exerçício máximo em bicicleta (4). Esses achados originaram a hipótese da existência de um “metaborreflexo inspiratório” ativado durante o exercício. Uma teoria confirmada no estudo subsequente, que comprovou a redistribuição do fluxo sanguíneo dos músculos periféricos ativos para o diafragma, correspondendo a mais de 14 - 16% do débito cardíaco (4). Além disso, a indução de fadiga muscular inspiratória através do esforço inspiratório intenso (resistência inspiratória = 60% da PImáx) e sustentado (razão entre o tempo inspiratório e duração total do ciclo respiratório [TI/TTot] = 0,70) aumentou a atividade nervosa simpática muscular (5) e reduziu o fluxo sanguíneo da perna inativa (6,7). Esses efeitos evidenciam a existência do metaborreflexo inspiratório (Figura 1).

O metaborreflexo inspiratório pode limitar o desempenho físico (10,20) quando o exercício ultrapassa 85% do $\dot{V}O_{2máx}$ devido à fadiga muscular inspiratória (18), que resulta na ativação do metaboreflexo (5,6), reduzindo o fluxo sanguíneo para os músculos esqueléticos ativos (4) e exarcebando a fadiga dos músculos periféricos (21). Por outro lado, a redução do trabalho muscular inspiratório (via assistência ventilatória) aumenta o tempo de exercício em 14 % (17) e atenua a fadiga do quadríceps ao exercício em ciclistas (21), provavelmente por inibir o metaborreflexo inspiratório.

Os efeitos do metaborreflexo inspiratório sobre o desempenho físico podem ser relevantes para indivíduos portadores de ICC e de DPOC. O estudo de Borghi-Silva et al. (12) mostra que a ventilação não-invasiva melhora a saturação periférica de O_2 e reduz a fadigabilidade do músculo quadríceps du-

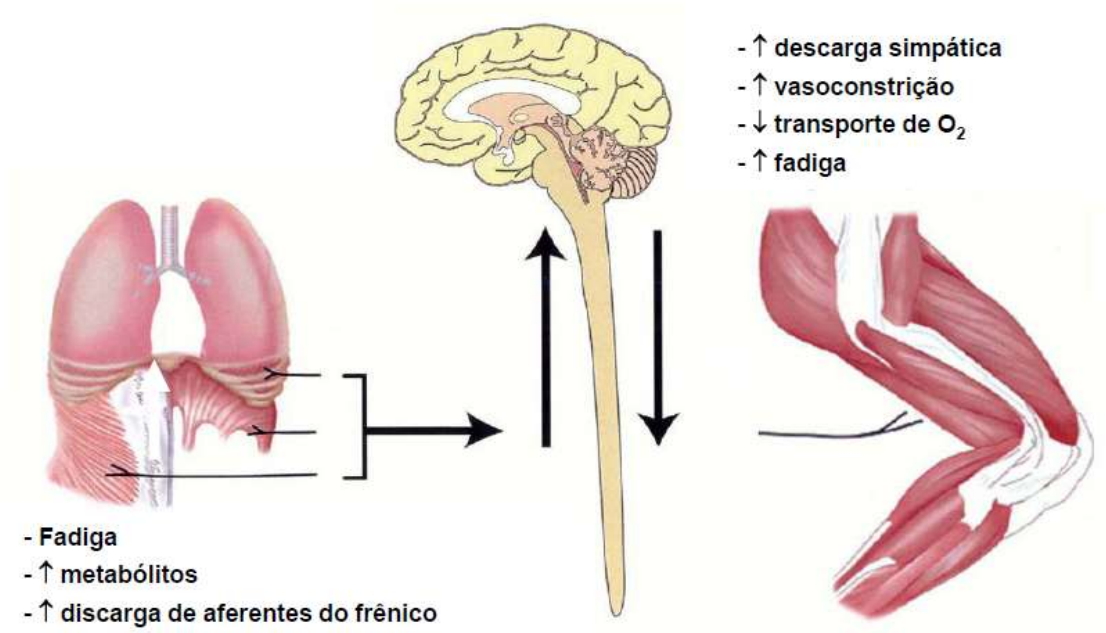

Figura 1. Ilustração esquemática do metaborreflexo inspiratório. O metaborreflexo inspiratório é ativado durante trabalho muscular inspiratório fatigante pelo acúmulo de metabólitos que aumenta a atividade de aferentes do frênico, resultando no aumento da atividade simpática e vasoconstrição periférica, exarcebando a fadiga dos músculos esqueléticos ativos. Adaptado de Dempsey et al. *Respir Physiol & Neurobiol*. 2006;151: 242-50.

rante exercício isocinético nos pacientes com DPOC. Esses dados sugerem que a ventilação não-invasiva poderia atenuar a ativação do metaborreflexo inspiratório. Nos pacientes com ICC, a redução do trabalho muscular inspiratório aumenta a tolerância ao exercício (11,22), melhora a oxigenação muscular periférica e reduz a concentração de lactato durante o exercício (11), provavelmente por redistribuir o fluxo sanguíneo dos músculos respiratórios para os locomotores (11). Portanto, é possível que intervenções que inibem o metaborreflexo inspiratório contribuam para o desempenho físico.

2.2 Treinamento muscular inspiratório e metaborreflexo inspiratório

O treinamento muscular inspiratório aumenta a força (2,23,24,25) e a resistência da musculatura inspiratória (2,23,24,25), além de reduzir a concentração de lactato durante o teste de resistência muscular inspiratória (26) e durante o exercício incremental (27,28). Dessa forma, é possível que o treinamento muscular inspiratório reduza o acúmulo de metabólitos durante o trabalho muscular inspiratório o que poderia atenuar a atividade do metaborreflexo (29).

De fato, o treinamento muscular inspiratório realizado a 50% da PImáx atenua a resposta pressora (30) e reduz a fadiga dos músculos flexores plantar durante ativação do metaborreflexo inspiratório em indivíduos saudáveis (31). Uma avaliação mais objetiva do metaborreflexo inspiratório mostrou que o treinamento muscular inspiratório ameniza a redução do fluxo sanguíneo na perna durante a indução do metaborreflexo em pacientes com ICC e portadores de fraqueza muscular inspiratória (8).

Outras evidências da associação entre condicionamento muscular e redução do metaborreflexo muscular foram relatadas em estudos envolvendo a musculatura esquelética. O treinamento de preensão manual reduz a produção de metabólitos e atenua a resposta pressora durante exercício isquêmico do antebraço (32). Reduções na atividade nervosa simpática muscular durante isquemia após exercício também foram observadas depois do treinamento de resistência do antebraço (33). Já em modelo animal de insuficiência cardíaca, o treinamento aeróbico melhora as respostas cardiovasculares à ativação do metaborreflexo, ou seja, o treinamento aumenta as respostas da pressão

arterial média e atividade nervosa simpática renal, que estão reduzidas nos ratos com insuficiência cardíaca comparado aos ratos saudáveis (34).

2.3 Treinamento aeróbico e desempenho muscular inspiratório

O treinamento aeróbico melhora o desempenho muscular respiratório (35,36), visto que atletas apresentam um aumento da resistência muscular inspiratória comparado aos indivíduos sedentários (36). Além disso, o treinamento de corrida aumenta a ventilação voluntária máxima em indivíduos previamente sedentários (37) e o treinamento de natação melhora a resistência muscular inspiratória representada pelo aumento da aréa total da PImáx e do tempo de fadiga (38). O exercício aeróbico regular também previne reduções na força muscular inspiratória relacionadas ao envelhecimento (39) e aumenta a força muscular inspiratória em pacientes com ICC e fraqueza muscular inspiratória (40).

Estudos em modelo animal demonstram que o treinamento aeróbico pode melhorar a capacidade oxidativa (41,42,43,44,45,46,47), aumentar a densidade capilar das fibras musculares do tipo I, tipo IIa e tipo IIb (42) e melhorar a capacidade anti-oxidante dos músculos inspiratórios (43,46,47), além de reduzir a fadiga do diafragma *in vitro* (46). Dessa forma, é possível que o exercício aeróbico crônico reduza o acumúlo de metabólitos durante o trabalho inspiratório fatigante com repercussões na ativação dos metaborreceptores.

3. Controle da ventilação durante o exercício

Durante o exercício, a ventilação pulmonar precisa ser aumentada para manter adequada a oxigenação e a remoção de CO_2 dos tecidos. O controle da ventilação durante o exercício é mediado principalmente pelos quimiorreceptores e metaborreceptores (13). Nos pacientes com ICC, a sensibilidade quimiorreflexa encontra-se anormalmente aumentada (48), prediz mortalidade (49) e participa da fisiopatogênese da hiperativação simpática (50) e dos padrões ventilatórios anormais em repouso (51), e possivelmente das respostas ventilatórias anormais ao exercício (52).

3.1 Quimiorreflexo central e periférico

Os quimiorreceptores centrais estão localizados na face ventral do bulbo e respondem a variações nas concentrações de CO_2 (Figura 2). Os quimiorreceptores periféricos localizam-se na artéria carótida comum e na artéria aorta e são sensíveis as variações na PO_2, PCO_2 e no pH do sangue arterial (14) (Figura 2). O quimiorreflexo central pode ser avaliado pela inalação de uma mistura hipercapnica (7% CO_2 e 93% O_2) durante 4 minutos (53). O quimiorreflexo periférico pode ser avaliado por diversos testes: pela hipóxia transitória plotando-se a ventilação máxima contra a menor saturação arterial de oxigênio ($SatO_2$) após a inalação de nitrogênio puro (54); pela inalação de 10% CO_2 em uma inspiração única, calculando-se a razão entre o aumento da ventilação e a alteração da pressão de CO_2 ao término da expiração (PET_{CO2}) (54,55,56); e pela inalação de uma mistura hipóxica (10% O_2 e 90% N_2)

durante 3 minutos (57,58). A ativação dos quimiorreceptores aumenta a atividade nervosa simpática, frequência cardíaca, pressão arterial e a ventilação minuto (59). Essas respostas podem estar profundamente alteradas na ICC.

3.2 Quimiorreflexo na insuficiência cardíaca

O aumento do quimiorreflexo periférico (48,53,60,61,62,63) e central (48,63,64) participam da fisiopatologia da ICC, contribuindo para a ativação simpática e padrões ventilatórios anormais (Figura 2). A inibição do quimiorreflexo periférico via hiperóxia reduz a atividade nervosa simpática muscular, sugerindo que anormalidades no controle quimiorreflexo levam à hiperatividade simpática (50). O aumento da atividade simpática induz vasoconstrição periférica que eleva a pós-carga ventricular direita e esquerda, piorando a função cardiorrespiratória. Além disso, o aumento da atividade quimiorreflexa pode estar relacionado com a gravidade da ICC. A atividade quimiorreflexa central está aumentada nos pacientes com classe funcional III NYHA comparada aos com classe funcional II NYHA (53) e pacientes com quimiorreflexo alterado (>0,72 $L.min^{-1}.\%SatO_2^{-1}$) podem apresentar reduzida capacidade funcional comparada com pacientes com quimiorreflexo normal (49,62).

O aumento do quimiorreflexo periférico também participa da gênese da ventilação oscilatória em repouso e está relacionado com apnéia central do sono. Pacientes com ICC e ventilação do tipo Cheyne-Stokes ou ventilação pe-

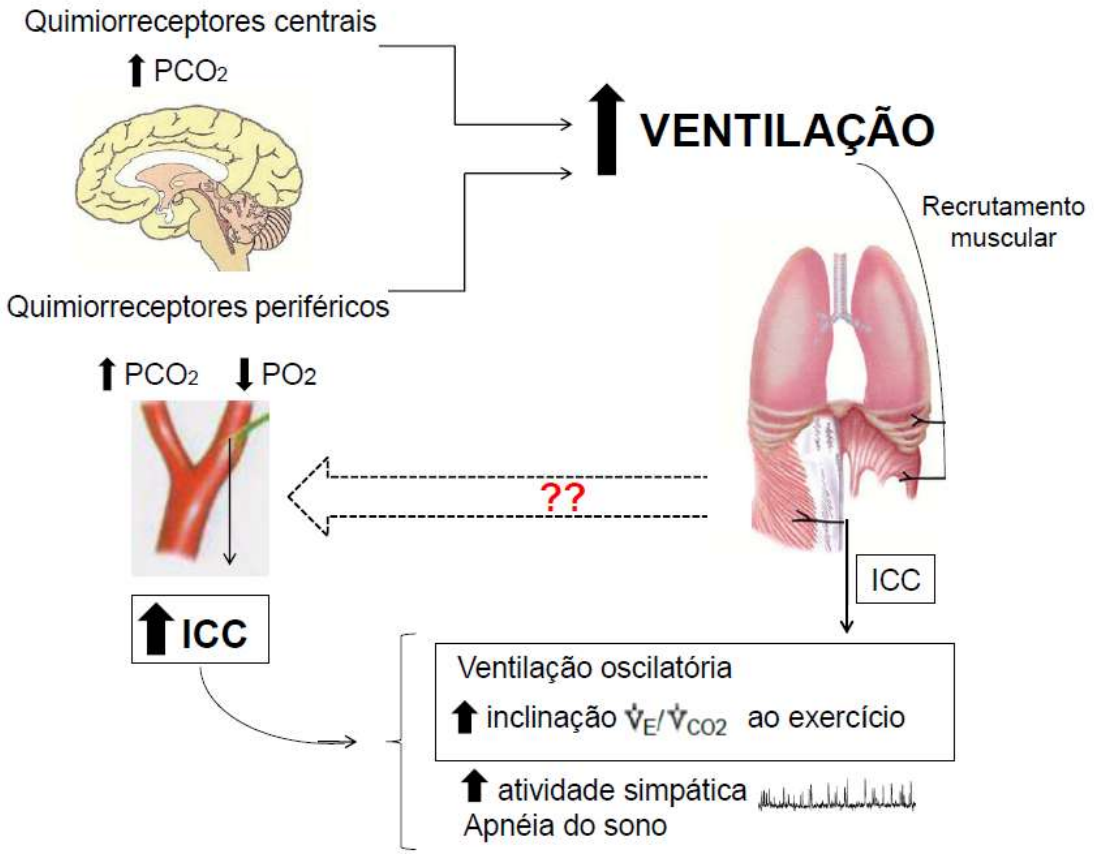

Figura 2. Ilustração esquemática do quimiorreflexo na ICC. Os quimiorreceptores centrais (localizados na face ventral do bulbo) sensibilizados pelo aumento da pressão parcial de CO_2 e os quimiorreceptores periféricos (localizados na artéria carótida comum e na artéria aorta) sensibilizados pelo aumento da pressão parcial de CO_2 (respostas rápidas) e pela redução da pressão parcial de O_2 (respostas lentas) aumentam a ventilação através do recrutamento dos músculos respiratórios. O quimiorreflexo central e o periférico estão aumentados na ICC. O quimiorreflexo periférico participa da fisiopatologia do aumento da atividade simpática, de padrões ventilatórios anormais como apnéia do sono, ventilação oscilatória em repouso e aumento da inclinação $\dot{V}_E/\dot{V}_{CO2}$ ao exercício. Como o treinamento da musculatura inspiratória reduz a ventilação oscilatória e a inclinação $\dot{V}_E/\dot{V}_{CO2}$ ao exercício na ICC, quimiorreflexo periférico e musculatura inspiratória poderiam estar associados na ICC (linhas tracejadas).

riódica apresentam maior sensibilidade quimiorreflexa do que pacientes com ventilação normal (51), mas a ventilação oscilatória em repouso pode ser normalizada pela inibição do quimiorreflexo periférico (51). O quimiorreflexo periférico pode ainda estar relacionado com apnéia do sono. O estudo de Solin et al., (65) mostrou uma associação entre o quimiorreflexo periférico (determinado pela técnica de uma inalação única de CO_2) e o índice de apnéia-hipoapnéia central nos pacientes com ICC. Portanto, o quimiorreflexo parece estar relacionado com alterações respiratórias em repouso e durante o sono. É possível que as alterações do quimiorreflexo também afetem as respostas ventilatórias ao exercício na ICC.

3.2.1 Quimiorreflexo nas respostas ventilatórias ao exercício

Pacientes com ICC podem apresentar respostas ventilatórias anormais ao exercício progressivo como o aumento da inclinação $\dot{V}_E/\dot{V}_{CO2}$ e a presença de ventilação oscilatória, ambos com repercussões prognósticas (66,67,68). Vários mecânismos foram propostos para explicar o aumento da inclinação $\dot{V}_E/\dot{V}_{CO2}$ incluindo o aumento do espaço morto, a acidose láctica precoce e a atividade anormal do quimiorreflexo e do metaborreflexo muscular esquelético (69). Na ICC o padrão pulmonar restritivo diminui o aumento do volume corrente, aumentando a frequência respiratória e a relação espaço morto/volume corrente. O descondicionamento físico, aumento do número de fibras musculares do tipo IIb e o limitado aumento do débito cardíaco podem favorecer a acidose láctica precoce ao exercício induzindo hiperventilação nos pacientes com ICC (69). As evidências mais fortes sugerem que as respostas

ventilatórias anormais ao exercício estão relacionadas com os mecanismos que controlam a ventilação como o quimiorreflexo (70) e o metaborreflexo muscular esquelético (70).

O quimiorreflexo periférico parece participar da fisiopatologia da hiperventilação ao exercício uma vez que a inibição do quimiorreflexo periférico (via di-hidrocodeína) reduz a inclinação $\dot{V}_E/\dot{V}_{CO2}$ durante o exercício progressivo (52). Além disso, os pacientes com elevação da inclinação $\dot{V}_E/\dot{V}_{CO2}$ (> 34) apresentam aumento da sensibilidade quimiorreflexa periférica e central (70). É possível que o metaborreflexo induza hiperventilação durante o exercício ou que ative o quimiorreflexo central (13). De fato, o metaborreflexo é um forte preditor da atividade quimiorreflexa central nos pacientes com ICC (48). Estudo recente demonstra que o quimiorreflexo central potencializa a resposta ventilatória induzida pelo metaborreflexo do antebraço em indivíduos saudáveis (71). É importante notar que ambos quimiorreflexo central (70) e resposta ventilatória induzida pelo metaborreflexo muscular esquelético se correlacionam significativamente com a inclinação $\dot{V}_E/\dot{V}_{CO2}$ durante o exercício progressivo na ICC (70). Além disso, pacientes com inclinação $\dot{V}_E/\dot{V}_{CO2}$ anormalmente elevada apresentam aumento da resposta ventilatória induzida pelo metaborreflexo muscular esquelético e redução da sensibilidade barorreflexa (70).

A ventilação oscilatória ao exercício pode estar relacionada com hiperatividade dos quimiorreceptores e metaborreceptores e com prolongamento do tempo circulatório (13). O aumento do tempo circulatório poderia retardar a detecção de alterações na pressão parcial dos gases

sanguíneos arteriais pelos quimiorreceptores levando a instabilidade respiratória (13). Estudo em humanos sugere que o quimiorreflexo periférico encontra-se envolvido na gênese das oscilações ventilatórias em repouso (51). É possível que as oscilações da ventilação ao exercício progressivo apresentem um mecanismo semelhante, no entanto essa teoria ainda necessita de confirmação. Alternativamente o metaborreflexo poderia contribuir com a ventilação oscilatória ao exercício, visto que pacientes com ICC e ventilação periódica apresentam um aumento da atividade metaborreflexa (48).

3.2.2 Músculos inspiratórios e respostas ventilatórias ao exercício

Os pacientes com ICC podem apresentar redução da força muscular inspiratória (72,73,74) estabelecida pela PImáx. Alguns estudos sugerem que a PImáx está associada com $\dot{V}O_{2pico}$ (73,75,76). No entanto, estudos mais recentes mostram fraca associação entre PImáx e $\dot{V}O_{2pico}$ (73). Além disso, os pacientes com fraqueza muscular inspiratória envolvidos nos estudos do nosso grupo de pesquisa apresentam capacidade funcional relativamente preservada (2,8,40,77). O treinamento muscular inspiratório que resulta em aumento da força muscular inspiratória reduz a inclinação $\dot{V}_E/\dot{V}_{CO2}$ e as oscilações ventilatórias ao exercício nos pacientes com ICC (2). Essas respostas ventilatórias ao exercício podem estar relacionadas com atenuação do quimiorreflexo (13). No entanto, ainda não há dados sobre os efeitos da força muscular inspiratória sobre o quimiorreflexo na ICC.

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ARTIGO I

Attenuated respiratory muscle metaboreflex in endurance-trained individuals

Atenuação do metaborreflexo respiratório em indivíduos treinados aerobicamente

Attenuated respiratory muscle metaboreflex in endurance-trained individuals

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Running head: Respiratory muscle metaboreflex in athletes

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Abstract

The respiratory muscle metaboreflex may limit physical performance in athletes. Since aerobic exercise training improves inspiratory muscle conditioning, we hypothesized that endurance trained individuals demonstrate a blunted respiratory muscle metaboreflex in comparison to sedentary individuals. We studied 9 runners (23 ± 0.7 years, (maximal oxygen uptake [$\dot{V}_{O_2max}$] = 53 ± 4 ml.kg^{-1}.min^{-1}) and 9 sedentary healthy volunteers (24 ± 0.7 years, $\dot{V}_{O_2max}$ = 37 ± 2 ml.kg^{-1}.min^{-1}). The respiratory muscle metaboreflex was assessed during fatiguing inspiratory muscle work induced by breathing against an inspiratory load of 60% maximal inspiratory pressure (PI_{max}), with prolonged duty cycle. Mean blood pressure, popliteal blood flow, and heart rate were measured throughout the protocol. Fatiguing inspiratory muscle work increased mean blood pressure in endurance trained (from 101 ± 3 to 110 ± 5 mmHg) and in sedentary individuals (from 96 ± 3 to 100 ± 4 mmHg). Leg blood flow was decreased in sedentary individuals (from 0.179 ± 0.01 to 0.141 ± 0.01 cm.s), but not in trained individuals (from 0.211 ± 0.02 to 0.214 ± 0.02 cm.s). Leg vascular resistance increased in sedentary (from 559 ± 35 to 757 ± 56 units), but did not change in active individuals (from 528 ± 69 to 558 ± 64 units). Changes in leg vascular resistance at task failure of the inspiratory effort were inversely related to $\dot{V}_{O_2max}$ (r = - 0.56, $p < 0.05$). The control protocol did not change mean pressure, leg blood flow or leg vascular resistance. These data demonstrate that endurance-trained individuals present an attenuated respiratory muscle metaboreflex.

Key words: inspiratory muscle, inspiratory muscle training, rehabilitation, physical performance.

Introduction

Fatiguing inspiratory muscle work induces sympathetically mediated vasoconstriction in skeletal muscle (1,2,3), a response that appears to be mediated by nerve fibers sensitive to metabolite accumulation (4,5,6). This respiratory muscle metaboreflex can generate vasoconstriction in inactive skeletal muscle (7) but also exercising muscle (8,9,10), limiting physical performance by diverting blood flow from active limbs to the respiratory muscles (11). A number of studies indicate that endurance training of the inspiratory muscles attenuates the respiratory muscle metaboreflex in young healthy individuals (12,13) as well as in patients with chronic heart failure (14).

Whole body aerobic exercise training may also improve inspiratory muscle performance. For example, the oxidative capacity of the diaphragm increases after aerobic exercise training in rats (15,16,17,18,19), and age-related reductions in inspiratory muscle strength are prevented by regular aerobic exercise in humans (20). In addition, aerobic exercise training increases inspiratory muscle endurance in previously sedentary young healthy individuals (21) and increases inspiratory muscle strength in patients with chronic heart failure (22). However, despite evidence suggesting that physical exercise improves inspiratory muscle conditioning, it is unknown if this translates into attenuation of the respiratory muscle metaboreflex. Based upon prior findings of greater oxidative capacity and endurance in inspiratory muscles after aerobic exercise training, we hypothesized that endurance trained individuals would demonstrate a blunted respiratory muscle metaboreflex in comparison to sedentary individuals.

Methods

Subjects and Design

This was a cross sectional study involving 18 healthy young individuals aged 21 to 29 years (mean 24 ± 0.5 years). Nine volunteers were active runners performing at least 150 min of exercise per week for at least three months (average 30 ± 12 months). Nine were sedentary individuals not involved in regular aerobic exercise for at least the past year. All subjects were non-smokers, non-obese, free of autonomic and cardiovascular diseases, and had no weight change greater than 5 kg in the 6 months prior to study. All subjects gave written informed consent prior to participation. The study was approved by the institutional review board at Spaulding Rehabilitation Hospital.

Pre-Study Evaluations

PI_{max} was assessed by a pressure transducer (Gould, Cleveland, Ohio, USA) during deep inspiration from residual volume against an occluded airway with a minor air leak (2 mm). The test was repeated several times to find 6 measurements with less than 10% variation (23). This measurement had a coefficient of variation of 3.9 ± 4% on two different days. All subjects were familiarized with the experimental protocol by breathing against an inspiratory load of 60% PI_{max} and with prolonged duty cycle (inspiratory time [TI]/total time [TTot] = 0.75]. This task was stopped before inducing inspiratory muscle fatigue.

Subsequently, $\dot{V}O_{2max}$ was determined by a maximal cardiopulmonary exercise test. Using a ramp protocol, subjects walked and ran on a treadmill,

while grade was increased every 2 min until exhaustion. $\dot{V}O_{2max}$ was assessed by online computer-assisted open circuit spirometry. Expired O_2 and CO_2 gas fractions were measured with paramagnetic O_2 and infrared CO_2 analyzers (TrueOne2004, East Sandy, Utah, USA). Ventilation was assessed by a Hans Rudolph 3813 pneumotachograph (Kansas City, MO, USA). Attainment of $\dot{V}O_{2max}$ was determined by meeting at least 3 of the following criteria: 1) O_2 uptake plateau despite increasing workload; 2) respiratory exchange ratio ≥ 1.10 at peak exercise; 3) achievement of age-predicted maximal heart rate; and 4) a rating of perceived exertion ≥ 19 on the Borg scale of 6 to 20.

Experimental Protocol

At least two days after the pre-study evaluation, the experimental protocol was performed in the morning in a temperature controlled room. All subjects were in a fasting state, avoided caffeinated beverages and alcohol for at least 12 hours, and exercise for at least 48 hours prior to study. First, PI_{max} was determined as described above to account for a potential learning effect. Subjects were instrumented in the supine position for the measurement of brachial blood pressure (Dinamap, DASH 2000, General Electric, Bloomfield, CT, USA), finger beat-by-beat blood pressure (Finapres, Ohmeda, Louisville, CO, USA), heart rate (standard lead II ECG), and popliteal blood flow. Popliteal blood flow was estimated via Doppler ultrasonography (Multidop T2, DWL, Singen, Mühlhausen-Ehingen, Germany) based on flow velocity through the arterial vessel. Briefly, a continuous wave 4 MHZ Doppler probe was placed against the skin under the knee to insonate the popliteal artery proximal to the

bifurcation. The signal was optimized and the waveform of the integrated Doppler-derived velocity was recorded as a measure of beat-by-beat popliteal flow. This approach has been validated by showing excellent agreement between Doppler and plethysmography derived flows (24) (r^2=0.93). In addition, inspiratory volume was assessed via pneumotachograph (Pneumotach 3700 series, Hans Rudolph, Kansas City, MI, USA), end-tidal partial pressure of CO_2 (PET_{CO2}) was measured via an infrared CO_2 analyzer (VacuMed, Ventura, CA, USA), and inspiratory pressure at the mouth was continuously assessed via a pressure transducer.

Baseline data were collected during 5 minutes of spontaneous breathing. Subsequently, fatiguing inspiratory muscle work, induced by breathing against an inspiratory load of 60% of PI_{max} and with prolonged duty cycle (TI/TTot = 0.75), was employed to assess the respiratory muscle metaboreflex (24). Subjects breathed continuously through a medium two-way valve (Hans Rudolph, 2600 series, Shawnee, KS, USA) connected to a POWER-breathe Inspiratory Muscle Trainer (Southam, United Kingdom) on the inspiratory side. Inspiratory pressure was continuously recorded and displayed on a computer screen. During each inspiratory effort, subjects were instructed to: 1) achieve the preset of target inspiratory pressure (60% PI_{max}) traced on the screen; 2) maintain a square wave inspiratory pressure throughout each inspiration; and 3) avoid inadvertent contraction of non-respiratory muscles. Breathing frequency (15 breaths per min) and duty cycle (TI/TTot = 0.75) were guided by a computer generated audio signal with distinct inspiratory and expiratory commands. Fatiguing inspiratory muscle work was continued for one minute beyond the

point of the task failure, the point at which the subject could not achieve or maintain the target inspiratory pressure despite continued verbal encouragement. Inspiratory effort was assessed by a 6 to 20-point Borg scale when fatiguing inspiratory work was interrupted. After 40 minutes of recovery, baseline data were collected during 5 minutes of spontaneous breathing followed by a control protocol of the same duration as the fatiguing work. An inspiratory load of 2% PI_{max} and a prolonged duty cycle (0.75) were used in the control protocol. Subjects mimicked the breathing pattern and tidal volume performed during fatiguing inspiratory muscle work. PET_{CO2} was maintained at eupneic levels during both fatiguing and control protocols via CO_2 addition into the inspiratory circuit.

Statistical Analyses

Descriptive data are presented as mean ± SE. Unpaired t-test was used to compare physical characteristics, PI_{max} and $\dot{V}O_{2max}$ between endurance trained and sedentary individuals. Hemodynamic and respiratory responses to fatiguing inspiratory muscle work and control protocol were evaluated by two-way analysis of variance for repeated measures. When indicated, multiple comparisons were performed using the Tukey *post hoc* test. Pearson correlation was used to evaluate the following associations: changes in leg vascular resistance during fatiguing inspiratory muscle work and $\dot{V}O_{2max}$; time to achieve task failure of the inspiratory effort and $\dot{V}O_{2max}$; and time to achieve task failure of the inspiratory effort and PI_{max}. Differences and relations were considered significant at $p < 0.05$.

Results

As expected, endurance trained individuals had higher $\dot{V}O_{2max}$ compared to sedentary, but the groups did not differ in inspiratory muscle strength (Table 1). All subjects were able to maintain a breathing frequency of 15 resp/min and a prolonged duty cycle for fatiguing and control protocols (Table 2 and Table 3). PET_{CO2} was maintained at eupneic levels during fatiguing and control protocols (Table 2 and Table 3), but there was a slightly reduction in PET_{CO2} in the first minute of fatiguing inspiratory muscle work. Inspiratory volume was increased

Table 1. Characteristics

	Trained (n=9)	**Sedentary (n = 9)**	***p***
Age (years)	23 ± 0.7	24 ± 0.7	0.38
Gender (male/female)	5/4	6/3	
Weight (kg)	66 ± 4	71 ± 4	0.36
Height (cm)	1.74 ± 0.03	1.70 ± 0.04	0.28
Inspiratory muscle strength			
PImax (cmH_2O)	115 ± 6	111 ± 8	0.68
$\dot{V}O_{2max}$ ($ml.kg^{-1}.min^{-1}$)	53 ± 4	37 ± 2	0.002

Data are presented as mean ± SE. PImax = maximal inspiratory pressure; $\dot{V}O_{2max}$ = maximal oxygen uptake.

during fatiguing inspiratory muscle work and control protocol in endurance trained and in sedentary individuals (Table 2 and Table 3).

Fatiguing inspiratory muscle work tended to induce task failure slightly later in the endurance trained (trained: 321 ± 132 s, sedentary: 252 ± 107 s, p = 0.26). Time to achieve task failure of the inspiratory effort was significantly correlated to $\dot{V}O_{2max}$ across all subjects (r = 0.47, $p < 0.05$), but there was no significant correlation between maximal inspiratory pressure and time to achieve task failure of the inspiratory effort (r = 0.09, $p > 0.05$). Inspiratory pressure expressed as area under a curve (PI AUC) was similarly reduced in trained and in sedentary individuals at task failure of the inspiratory effort (Table 2). Furthermore, at task failure of inspiratory effort, both endurance trained and sedentary individuals reached similar Borg rating scale for effort (16 ± 2 and 16 ± 3). During the control protocol there was no significant change in inspiratory pressure (Table 3).

Fatiguing inspiratory work increased mean blood pressure and heart rate throughout the bout similarly in trained and sedentary individuals (Figure 1). Leg blood flow was decreased in the sedentary individuals (-18 ± 4%), whereas it was not changed in the endurance trained athletes [(4 ± 5%) Figure 1]. In one sedentary individual it was not possible to assess leg blood flow at task failure of the inspiratory effort. Leg vascular resistance was increased in sedentary individuals by fatiguing inspiratory muscle work and the increase averaged ~

Table 2. Respiratory variables during fatiguing inspiratory muscle work (60% PImax)

	Baseline	1 min	2 min	End
BF (resp/min) [a]				
Trained	12.13 ± 1.02	15 ± 0*	15.44 ± 0.18*†	15.56 ± 0.18*†
Sedentary	10.09 ± 1.3	14.78 ± 0.15*	15.56 ± 0.18*†	15.44 ± 0.18*†
IV (ml) [a,b]				
Trained	674 ± 100	799 ± 89*	827 ± 90*	909 ± 120*
Sedentary	635 ± 33	724 ±91*	652 ± 72*	613 ± 51*
PET_{CO2} (mmHg)[a]				
Trained	39 ± 2†	37 ± 2	40 ± 3†	40 ± 2†
Sedentary	37 ± 2†	34 ± 2	37 ± 2†	38 ± 3†
TI/Ttot				
Trained	0.43 ± 0.02	0.75 ± 0.02*	0.75 ± 0.02*†	0.76 ± 0.02*
Sedentary	0.46 ± 0.05	0.70 ± 0.02*	0.68 ± 0.03*†	0.70 ± 0.02*
PI Peak (cmH_2O) [a]				
Trained	- 1.6 ± 0.2	- 68 ± 3*	- 66 ± 3*	- 66 ± 3*
Sedentary	- 1.8 ± 0.9	- 66 ± 5*	- 65 ± 6*	- 65 ± 6*
PI AUC ($cmH_2O.s$)[a]				
Trained	25975 ± 3270	1426986± 107258*	1334778 ± 101155*	1317233 ± 98599*†
Sedentary	61170 ± 23223	1134549 ± 169782*	1054016 ± 165566*	1019040 ± 162060*†

Data are presented as mean ± SE. BF (breathing frequency); IV (inspiratory volume); TI/TTot (inspiratory time/total time); PI Peak (peak inspiratory pressure); PI AUC (inspiratoty pressure expressed as area under a curve); a) time effect; b) group effect; * $p < 0.05$ vs Baseline;† $p < 0.05$ vs 1 min; ‡ $p < 0.05$ vs 2 min.

Table 3. Respiratory variables during control protocol (2% PImax)

	Baseline	1 min	2 min	End
BF (resp/min) [a]				
Trained	11.63 ± 1.04	15.11 ± 0.35*	15.22 ± 0.15*	15.78 ± 0.22*†‡
Sedentary	10.14 ± 1.08	14.67 ± 0.23*	15.11 ± 0.11*	15.89 ± 0.20*†‡
IV (ml) [a]				
Trained	703 ± 130	991 ± 139*	1054 ± 145*	966 ± 103*
Sedentary	593 ± 29	760 ± 82*	716 ± 62*	745 ± 79*
PET_{CO2} (mmHg)				
Trained	40 ± 2	39 ± 3	38 ± 3	39 ± 2
Sedentary	37 ± 2	35 ± 3	37 ± 2	36 ± 2
TI/TTot [a]				
Trained	0.43 ± 0.03	0.61 ± 0.02*	0.61 ± 0.02*	0.61 ± 0.03*
Sedentary	0.47 ± 0.02	0.62 ± 0.04*	0.63 ± 0.04*	0.62 ± 0.05*
PI Peak (cmH_2O) [a]				
Trained	- 1.4 ± 0.2	- 2 ± 0.4*	- 2 ± 0.4*	- 2 ± 0.3
Sedentary	- 1.2 ± 0.8	- 3 ± 1.2*	- 4 ± 2*	- 4 ± 2
PI AUC ($cmH_2O.s$)				
Trained	25085 ± 4687	37320 ± 5005	39358 ± 5497	36174 ± 4817
Sedentary	55311 ± 17537	62793 ± 13071	72923 ± 25896	61940 ± 15711

Data are presented as mean ± SE. BF (breathing frequency); IV (inspiratory volume); TI/TTot (inspiratory time/total time); PI Peak (peak inspiratory pressure); PI AUC (inspiratoty pressure expressed as area under a curve); a) time effect; * $p < 0.05$ vs Baseline;† $p < 0.05$ vs 1 min; ‡ $p < 0.05$ vs 2 min.

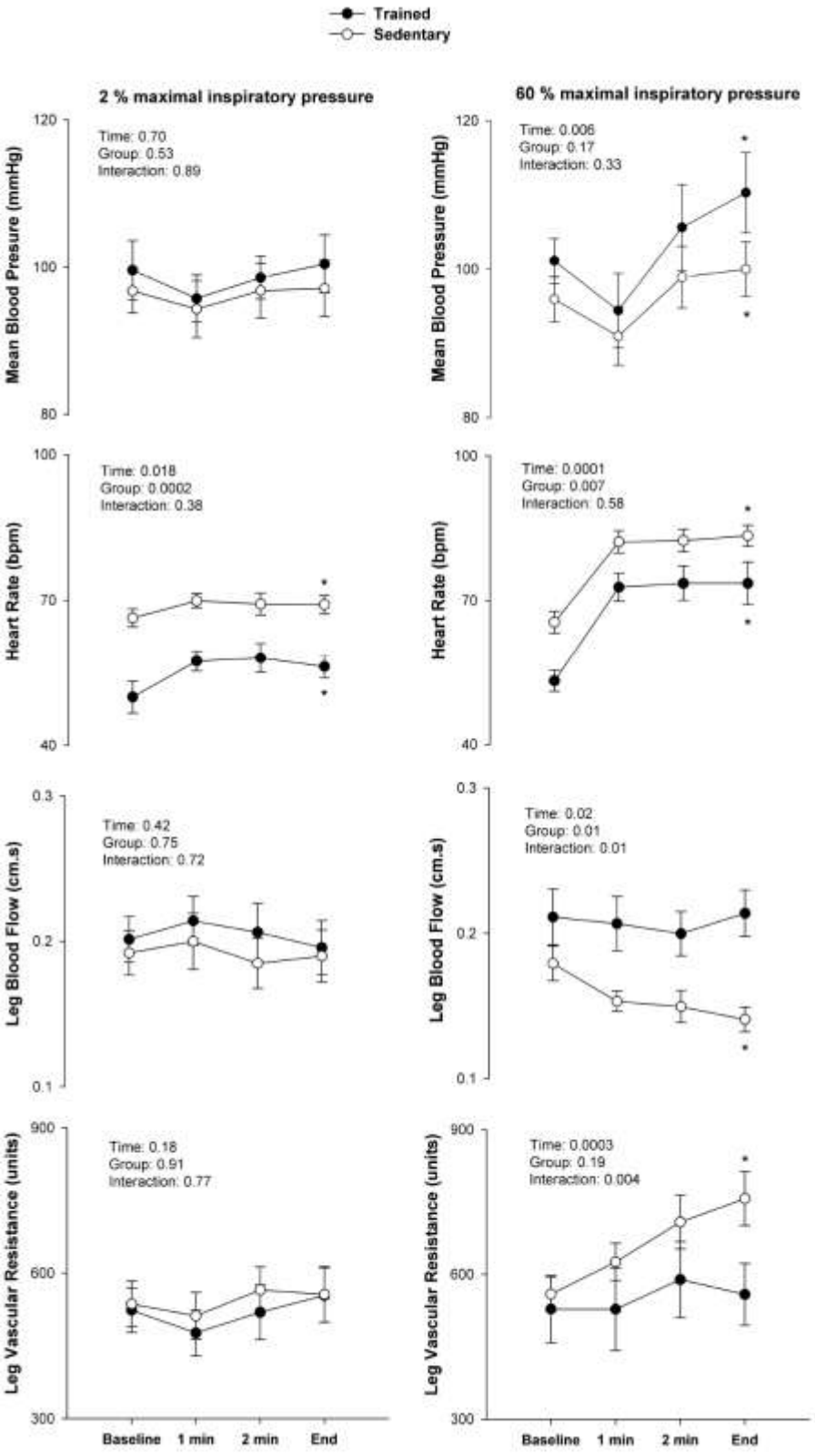

Figure 1. Haemodynamic effects of fatiguing inspiratory muscle work and control protocol in endurance trained and sedentary individuals. Values are mean ± SE. Two-way analysis of variance for repeated measures was performed to compared baseline and the last minute of inspiratory muscle work corresponding to task failure of the inspiratory effort. * Significantly different from baseline ($p < 0.05$).

33%. In contrast, leg vascular resistance presented no significant changes in endurance-trained individuals (Figure 1). Examination of the relation between $\dot{V}O_{2max}$ and the vascular resistance response to fatiguing inspiratory muscle work showed that, across all subjects, the magnitude of the peripheral vasoconstriction was inversely related to $\dot{V}O_{2max}$ (r = - 0.56, $p < 0.05$, Figure 2). In contrast, the control protocol did not significantly change mean pressure, leg blood flow or leg vascular resistance in either group, only heart rate was slightly increased (Figure 1).

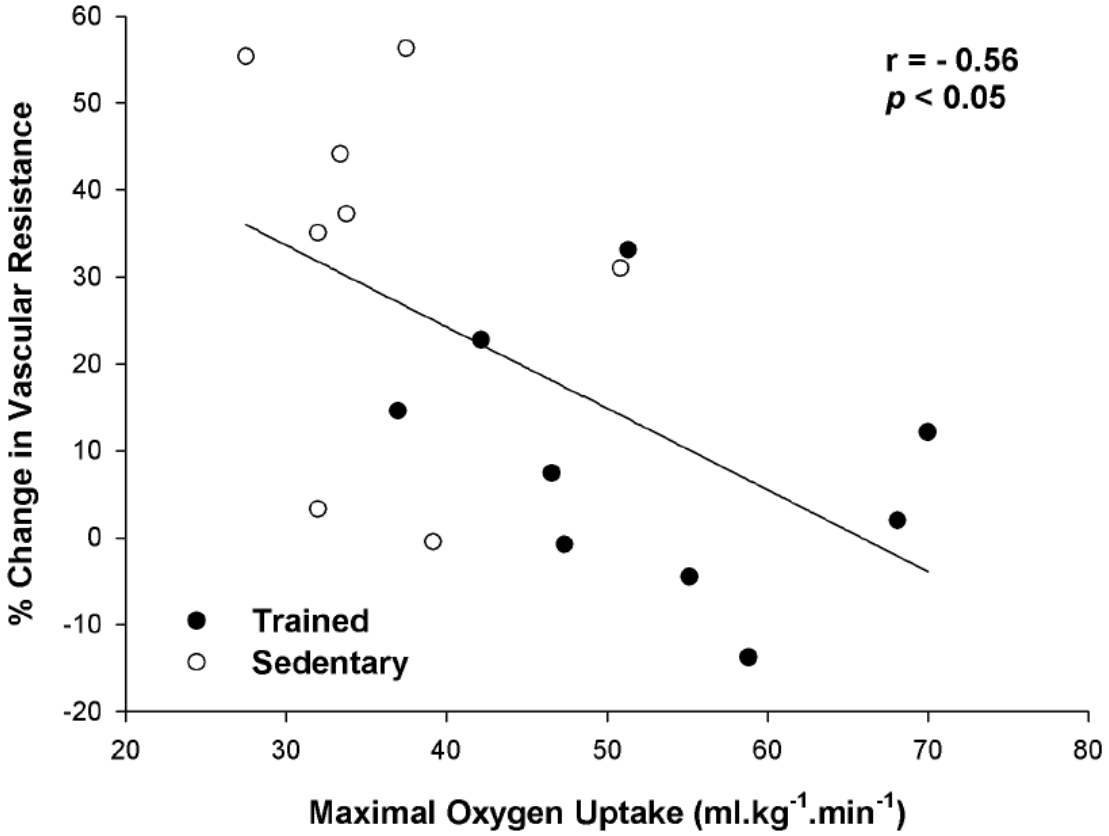

Figure 2. Relationship between $\dot{V}O_{2max}$ and percentage of change in leg vascular resistance during fatiguing inspiratory muscle work.

Discussion

Consistent with previous findings (1,2), our experiments showed that sedentary individuals presented an increase in leg vascular resistance with fatiguing inspiratory muscle work. In contrast, endurance-trained subjects had no significant increase in leg vascular resistance with fatiguing inspiratory muscle work. In addition, we found that maximal aerobic power across all subjects was inversely related to the peripheral vasoconstrictor response to inspiratory metaboreflex activation. These findings are in agreement with our working hypothesis that endurance-trained individuals have a blunted respiratory muscle metaboreflex.

The findings of the present cross sectional study suggest that whole body endurance training blunts the inspiratory muscle metaboreflex. However, the mechanisms responsible for this effect are not readily apparent. Previous studies have shown that, in healthy individuals, inspiratory muscle training results in attenuation of the respiratory muscle metaboreflex (12,13). Likewise, our group has previously shown that patients with heart failure and inspiratory muscle weakness have an exacerbated vasoconstrictor response to fatiguing inspiratory muscle work and that inspiratory muscle training improves limb blood flow under inspiratory loading in these patients (14). Therefore, it is concievable that whole body aerobic training might improve inspiratory muscle conditioning, resulting in reduced metabolite accumulation during fatiguing inspiratory work and consequent attenuation of the respiratory muscle metaboreflex. In fact, there is evidence that aerobic exercise training increases tissue oxidant and antioxidant capacity (15,16,17,18,19,25) and improves capillary density (17) of

the inspiratory muscles. In addition, aerobic exercise training reduces the rate of diaphragm fatigue in vitro (19) and prevents age-related reductions in inspiratory muscle strength (20). Moreover, regular running exercise (21) increases respiratory muscle endurance in previously sedentary subjects and swimming training also increases inspiratory muscle endurance, as indicated by increases in the time to fatigue and in the total area of sustained PI_{max} (26).

Our endurance-trained individuals could have greater inspiratory muscle endurance than sedentary individuals. Although we did not perform an endurance test of the inspiratory muscles (23), endurance-trained individuals tended to show a slightly later task failure of the inspiratory muscles during fatiguing inspiratory muscle work. Likely, whole body exercise increases the inspiratory muscle work via greater ventilatory requirement leading to inspiratory muscle conditioning. For example, ventilatory muscle training at 60% of PI_{max} increases respiratory muscle endurance and attenuates the increment in blood lactate concentration during respiratory endurance test (27). If this finding is applicable for regular aerobic exercise, reduced lactate accumulation during fatiguing inspiratory muscle work could account for attenuated inspiratory metaboreflex. This hypothesis is also supported by data which indicate that handgrip exercise training reduces metabolite accumulation, blunting blood pressure responses during ischemic exercise (28). Furthermore, muscle sympathetic nerve activity after forearm ischemia is attenuated by the forearm endurance training (29).

Our findings may have practical implications. An attenuated inspiratory metaboreflex in endurance-trained individuals could affect physical

performance. In fact, we found an inverse correlation between $\dot{V}O_{2max}$ and percentage of change in leg vascular resistance during fatiguing inspiratory muscle work. Thus, the most fit individuals demonstrate the most attenuated response to fatiguing inspiratory work. In previous study, increasing the work of breathing during maximal exercise reduced leg blood flow in cyclists (11). On the other hand, unloading the inspiratory muscles increased time performance during maximal cycle exercise (10) and prevented exercise-induced quadriceps fatigue in endurance-trained cyclist (30). These data suggest that the attenuation of the inspiratory metaboreflex can improve physical performance even in endurance-trained individuals. Furthermore, an attenuated inspiratory metaboreflex could explain the fact that inspiratory muscle training fails to increase physical performance in runners (31) and in well-trained athletes (32).

Our study has several limitations. First, we did not measure inspiratory muscle endurance. In agreement with previous findings (33), our sedentary and trained individuals had similar inspiratory muscle strength, as assessed by PImax., but inspiratory muscle endurance could have been different between the groups and this should be evaluated in future studies. Second, we did not assess diaphragm fatigue in this study. However, we considered reductions in mouth pressure as representative of task failure of the inspiratory muscles, as previously demonstrated (1,2,3,14). Finally, the cross sectional design of the present study indicates that our findings should be confirmed by prospective trials on the effects of whole body aerobic training on the inspiratory muscle metaboreflex.

Conclusion

Fatiguing inspiratory muscle work-induced peripheral vasoconstriction is attenuated in endurance-trained individuals, suggesting that regular aerobic exercise blunts the inspiratory muscle metaboreflex.

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ARTIGO II

Augmented peripheral chemoreflex in patients with heart failure and inspiratory muscle weakness.

Aumento do quimiorreflexo periférico em pacientes com insuficiência cardíaca e fraqueza muscular inspiratória

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Augmented peripheral chemoreflex in patients with heart failure and inspiratory muscle weakness☆

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ABSTRACT

We hypothesized that heart failure patients with inspiratory muscle weakness (IMW) present greater peripheral chemoreflex responsiveness and augmented exercise ventilatory oscillation compared to patients with preserved inspiratory muscle strength. We studied 19 heart failure patients: 9 with IMW (maximal inspiratory pressure [PImax] < 70% of predicted) and 10 with preserved inspiratory muscle strength. Inspiratory muscle strength was measured via pressure transducer. Peripheral chemoreflex was evaluated by the single-breath CO_2 test. Exercise ventilatory oscillation was determined as the ratio between amplitude and mean of each oscillation during incremental exercise. Patients with IMW had greater peripheral chemoreflex response (0.11 ± 0.03 l min^{-1} Torr^{-1}) than those with preserved inspiratory muscle strength (0.07 ± 0.03 l min^{-1} Torr^{-1}, $p = 0.02$). Moreover, there was a significant and inverse correlation between PImax and peripheral chemoreflex response ($r = -0.57$, $p = 0.01$). Likewise, there was a significant and inverse correlation between PImax and ventilatory oscillations ($r = -0.46$, $p = 0.04$). Our findings indicate that IMW is linked to increased peripheral chemoreflex and augmented exercise ventilatory oscillation in patients with chronic heart failure.

1. Introduction

Patients with chronic heart failure (CHF) may present abnormal ventilatory response to incremental exercise, including an increased slope of ventilation *vs.* carbon dioxide production ($\dot{V}_E/\dot{V}_{CO_2}$ slope) as well as periodic breathing, and both of these findings have prognostic value (Ribeiro et al., 2006). Several pathophysiological mechanisms have been proposed to explain these ventilatory patterns and a chemoreflex deregulation seems to participate in both (Tumminello et al., 2007). Another ventilatory abnormality with prognostic impact in CHF is inspiratory muscle weakness (IMW) (Frankenstein et al., 2008), which may be related to impaired limb blood flow, most likely due to an abnormal activity of the inspiratory muscle metaboreflex (Chiappa et al., 2008). Interestingly, we have previously shown that in patients with CHF and IMW, inspiratory muscle training improves ventilatory responses to exercise, with reduction in $\dot{V}_E/\dot{V}_{CO_2}$ slope and ventilatory oscillations (Dall'Ago et al., 2006; Ribeiro et al., 2009; Stein et al., 2009; Winkelmann et al., 2009). This effect of inspiratory muscle training on ventilatory responses associated with overactivity of chemoreflex suggests that inspiratory muscle strength and chemoreflex response could be associated in CHF. Therefore, the purpose of this study is to test the hypothesis that patients with CHF and IMW may have an augmented peripheral chemoreflex response when compared to patients with preserved inspiratory muscle strength.

2. Methods

2.1. Patients

We studied 19 patients with stable CHF due to left ventricular systolic dysfunction. Since current evidence suggests that patients with CHF with IMW respond better to inspiratory muscle training than patients without IMW (Arena et al., 2009; Chiappa et al., 2008; Dall'Ago et al., 2006; Ribeiro et al., 2009; Stein et al., 2009; Winkelmann et al., 2009), we evaluated two groups of patients: 9 with IMW (maximal inspiratory pressure [PImax] < 70% of predicted for age and gender [Neder et al., 1999]) and 10 with preserved inspiratory muscle strength. All patients had left ventricular ejection fraction less than 40%, had no history of angina or pulmonary disease, and were not obese or smokers. The protocol

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was approved by the Committee for Ethics in Research of the Hospital de Clínicas de Porto Alegre, and all patients signed an informed consent form. For all patients, measurement of inspiratory muscle strength, peripheral chemoreflex evaluation, and cardiopulmonary exercise test were obtained. Investigators responsible for each of the methods were not aware of the results of the other evaluations.

2.2. Measurement of maximal inspiratory pressure

PImax was measured with a pressure transducer (MVD-500 V.1.1 Microhard System, Globalmed, Porto Alegre, Brazil) during deep inspiration from residual volume against an occluded airway with a minor air leak (2 mm), as previously described (Dall'Ago et al., 2006; Chiappa et al., 2008; Winkelmann et al., 2009). The test was repeated at least 12 times to find 6 measurements with less than 10% of variation (American Thoracic society/European Respiratory Society, 2002).

2.3. Peripheral chemoreflex

Fast peripheral chemoreflex responsiveness was evaluated by the single-breath CO_2 test, as previously described (McClean et al., 1988; Martinez, 2008). Patients rested for 15 min in the supine position and breathed throughout a T-valve connected to a 6-liter reservoir bag containing 13% CO_2 in air. The T-valve was turned during the expiratory phase of the previous breath so that the subject inhaled a single breath of 13% CO_2 in air. $\dot{V}_E$ and end-tidal partial pressure of CO_2 (PET_{CO_2}) were analyzed breath-by-breath (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany). Peripheral chemoreflex responsiveness was determined by the ratio between the change in ventilation and the change in PET_{CO_2} during the first 20 seconds after exposure and was expressed in liters per minute per Torr ($l\,min^{-1}\,Torr^{-1}$). At least 10 tests were applied at 2 min intervals. To evaluate reproducibility, the single-breath CO_2 test was repeated in 7 patients after one week.

2.4. Cardiopulmonary exercise testing

Maximal incremental exercise test was performed on a treadmill (INBRAMED 10200, Porto Alegre, Brazil) using a ramp protocol, starting at a speed of 2.4 km h^{-1} and 2% slope, with 20-s increments of speed and slope to reach volitional fatigue at approximately 10 min, as previously described (Dall'Ago et al., 2006). Gas exchange variables were measured breath-by-breath by a validated system (Metalyzer 3B, CPX System, Cortex, Leipzig, Germany) (Meyer et al., 2001). Heart rate was determined using the R–R interval from a 12-lead electrocardiogram. Cardiopulmonary exercise variables were calculated as previously described (Dall'Ago et al., 2006). In short, peak oxygen uptake ($\dot{V}_{O_2}$ peak) was defined as the highest value achieved during the test for 20 seconds. $\dot{V}_E/\dot{V}_{CO_2}$ slope was obtained by linear regression model using all data points obtained during the exercise test. The quantification of ventilatory oscillations was performed as originally proposed by Francis et al. (1999) and modified by Dall'Ago et al. (2006). For every 2 adjacent 20-s period of $\dot{V}_E$, the amplitude of oscillation was calculated as difference between the 2 points divided by their mean. This value was again divided by the mean to obtain the relative amplitude, and the values of the entire cardiopulmonary test were averaged to convey in a single ratio. Therefore, similarly to what was done in our previous studies on inspiratory muscle training (Dall'Ago et al., 2006; Winkelmann et al., 2009), we quantified ventilatory oscillations during incremental exercise, but we did not evaluate the presence of periodic breathing, as done in other investigations (Agostoni et al., 2008; Ribeiro, 2006).

2.5. Statistical analysis

Descriptive data are presented as mean ± SD. Considering that inspiratory muscle strength as measured by PImax is a continuous variable and that from the clinical point of view it is useful to classify patients with or without IMW, we performed two analyses. First, groups were compared by the Student's *t*-test and afterwards the Pearson correlation coefficient was used to evaluate associations using the whole sample. Finally, stepwise multiple regression was used to predict peripheral chemoreflex responsiveness, using as regressors variables which presented correlations with p values less than 0.1 in the univariate analysis. Statistical significance for the other tests was set at $p < 0.05$.

3. Results

Table 1 presents the clinical characteristics as well as the results of inspiratory muscle strength, peripheral chemoreflex, and exercise responses for patients with and without IMW. The groups were similar in respect to age, gender distribution, height, weight, etiology, use of medications, and left ventricular ejection fraction. As by protocol, patients with IMW had lower PImax. $\dot{V}_{O_2}$ peak and $\dot{V}_E/\dot{V}_{CO_2}$ were not significantly different between the groups. Exercise ventilatory oscillation tended to be greater in patients with IMW than in those with preserved inspiratory muscle strength ($p = 0.1$).

The coefficient of variation for the single-breath CO_2 test in two different days was 13 ± 11%. Peripheral chemoreflex responsiveness was significantly increased in patients with IMW compared those with preserved inspiratory muscle strength (Table 1). As shown in Fig. 1, there was a significant inverse correlation between the peripheral chemoreflex response and PImax expressed in absolute units (panel a) as well as in percentage of predicted (panel b). PImax was also significantly and inversely correlated with exercise ventilatory oscillation (Fig. 1 panels c and d). Peripheral chemoreflex responsiveness was not significantly associated with $\dot{V}_{O_2}$ peak ($r = 0.18$, $p = 0.46$), with $\dot{V}_E/\dot{V}_{CO_2}$ ($r = -0.08$, $p = 0.74$) or with exercise ventilatory oscillation ($r = 0.35$, $p = 0.15$). By stepwise multiple regression analysis, PImax was the only independent predictor of peripheral chemoreflex ($p < 0.05$).

4. Discussion

An augmented peripheral chemoreflex is a common finding in CHF patients and may occur in as many as 40% of patients (Chua et al., 1997). The increased chemoreflex may be linked to abnormal ventilatory responses to exercise such as an increased $\dot{V}_E/\dot{V}_{CO_2}$ and exercise periodic breathing (Tumminello et al., 2007). IMW is also frequently found, occurring in more than 30% of our outpatients in a specialized heart failure clinic (Dall'Ago et al., 2006; Ribeiro et al., 2009), but the clinical characteristics associated with this ventilatory abnormality are not well defined. This small, cross-sectional study demonstrates, for the first time, that inspiratory muscle strength, as determined by PImax, is associated with augmented peripheral chemoreflex responsiveness and exercise ventilatory oscillation in CHF patients.

The augmented peripheral chemoreflex responsiveness in patients with IMW in the present study may not be attributed to disease severity, since both groups showed similar $\dot{V}_{O_2}$ peak and left ventricular ejection fraction. Moreover, in our patients, inspiratory muscle strength was found to be an independent predictor of peripheral chemoreflex responsiveness by multivariate analysis. Indeed, the link between peripheral chemoreflex and $\dot{V}_{O_2}$ peak has not been a consistent finding in previous studies (Ponikowski et al., 2001a). A modest association has been described between periph-

Table 1
Clinical characteristics, inspiratory muscle strength and results of the cardiopulmonary exercise test.

	Inspiratory muscle weakness (n = 9)	Preserved inspiratory muscle strength (n = 10)	p
Age (years)	52 ± 7	57 ± 9	0.21
Gender (male/female)	7/2	9/1	
Weight (kg)	74 ± 17	76 ± 15	0.73
Height (cm)	164 ± 9	165 ± 6	0.85
Etiology (n):			
Ischemic	5	4	
Non-ischemic	4	6	
Medication (n):			
Digoxin	5	5	
ACE-inhibitors	9	10	
Beta-blockers	8	9	
Diuretics	9	10	
Left ventricular ejection fraction (%)	36 ± 9	34 ± 10	0.57
Inspiratory muscle strength			
Pimax (cm H_2O)	65 ± 15	124 ± 23	0.0001
Pimax (% of predicted)	55 ± 12	113 ± 22	0.0001
Peripheral chemoreflex			
Single-breath CO_2 test (l min^{-1} $Torr^{-1}$)	0.11 ± 0.03	0.07 ± 0.03	0.02
Cardiopulmonary exercise test $\dot{V}_{O_2}$ peak (ml kg^{-1} min^{-1})	22 ± 5	20 ± 4	0.42
$\dot{V}_E/\dot{V}_{CO_2}$ slope	35 ± 4	34 ± 6	0.73
Exercise ventilatory oscillations	0.059 ± 0.017	0.047 ± 0.011	0.10

Data are presented as mean ± SD. ACE: angiotensin-converting enzyme; Pimax: maximal inspiratory pressure; $\dot{V}_{O_2}$ peak: peak oxygen uptake; $\dot{V}_E/\dot{V}_{CO_2}$ slope: slope of ventilation vs. carbon dioxide production.

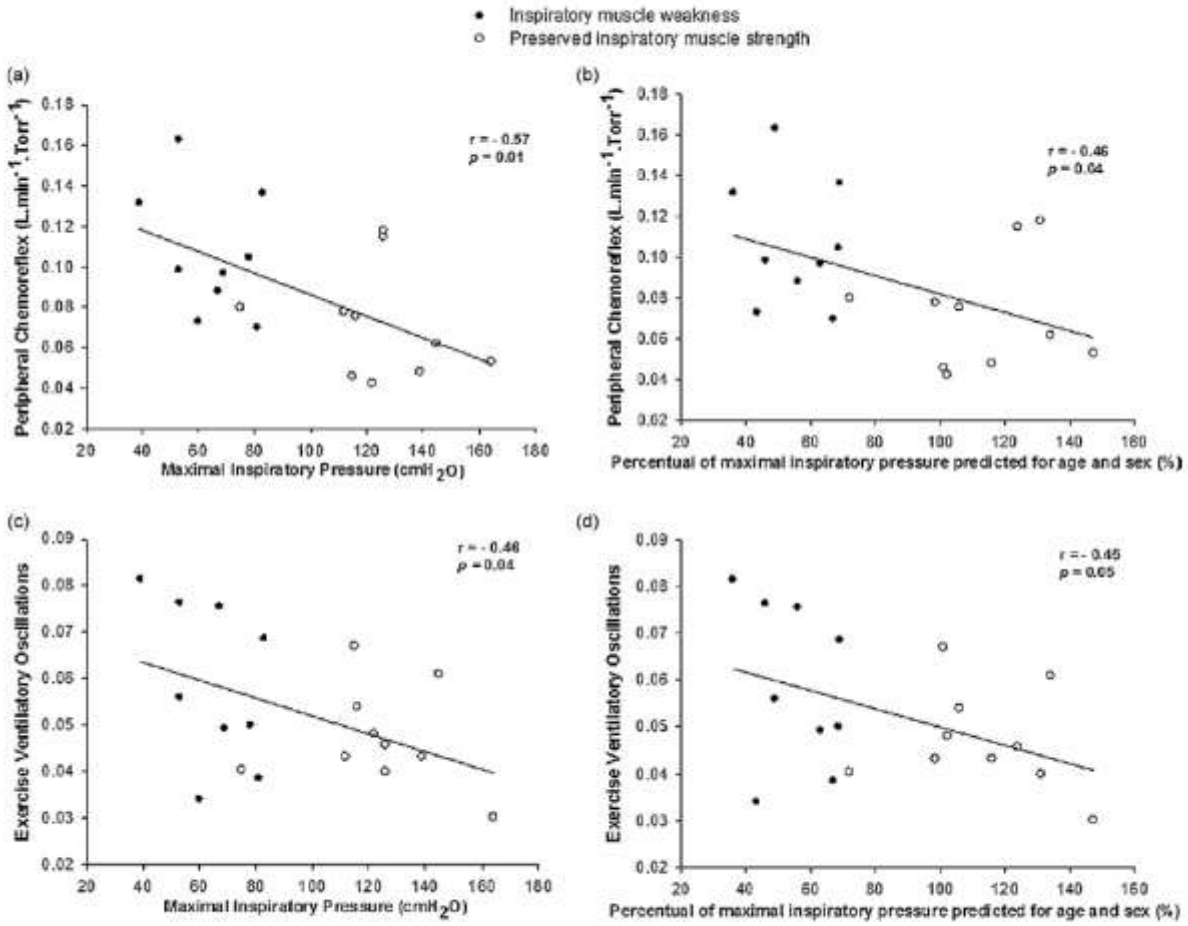

Fig. 1. Scatter plots for the associations between maximal inspiratory pressure (expressed in absolute values and as percentage of predicted), peripheral chemoreflex response, and exercise ventilatory oscillations. Open circles represent patients with preserved inspiratory muscle strength and closed circles represent patients with inspiratory muscle weakness.

eral chemosensitivity assessed by the transient hypoxic method and $\dot{V}_E/\dot{V}_{CO_2}$ slope during exercise (Ponikowski et al., 2001a,b), but not when evaluated by the single-breath CO_2 test (Chua et al., 1996).

Although peripheral chemoreflex may be involved in the pathogenesis of resting periodic breathing (Ponikowski et al., 1999), there are limited data exploring the relationship between peripheral chemoreflex and exercise ventilatory oscillation. In our study, there was no significant correlation between peripheral chemoreflex responsiveness and exercise ventilatory oscillation. An augmented metaboreflex could account for exercise ventilatory oscillation by itself or via increased central chemoreflex sensitivity (Piepoli et al., 1999; Ponikowski et al., 2001c). However, ergoreflex-induced ventilatory responses to exercise are only linked to central chemoreflex, but not to peripheral chemoreflex sensitivity (Ponikowski et al., 2001c). In addition, patients with periodic breathing have shown greater ergoreflex-induced ventilatory response to exercise (Ponikowski et al., 2001c).

The inspiratory metaboreflex engaged during fatiguing inspiratory muscle work is augmented in CHF patients with IMW (Chiappa et al., 2008). Thus, exercise-induced inspiratory muscle fatigue and metabolite accumulation could activate chemically sensitive afferents innervating diaphragm. Since exercise-induced diaphragm fatigue results in sympathoexcitation (St Croix et al., 2000), CHF patients with inspiratory muscle weakness might have augmented peripheral chemoreflex and/or exercise oscillatory ventilation via increased sympathetic activity (Di Vanna et al., 2007; Piepoli et al., 1999). This contention is supported by our recent finding that inspiratory muscle training blunts the inspiratory muscle metaboreflex, as demonstrated by the improvement in limb blood flow under inspiratory loading in resting and in exercising muscles (Chiappa et al., 2008). Moreover, preliminary data from Mello et al. (2008) have also shown that inspiratory muscle training in patients with CHF and IMW reduces central and peripheral sympathetic activity.

The present cross-sectional study has several limitations. First, the sample size is relatively small to detect weaker associations. Second, we only evaluated the peripheral component of the chemoreflex response to CO_2. A more comprehensive evaluation of the chemoreflex, such as that performed by Giannoni et al. (2009), could have resulted in better understanding of its role in ventilatory responses to exercise and this should be done in future studies. Third, we did not select patients with exercise-induced periodic breathing as described in previous studies (Agostoni et al., 2008; Ribeiro, 2006), but we evaluated the oscillations in the ventilatory response to exercise using the method originally developed by Francis et al. (1999). Therefore, our methodology is inappropriate to determine the role of peripheral chemoreflex in exercise-induced periodic breathing.

Our findings have potential clinical implications. Chemoreflex responsiveness, inspiratory muscle strength, and exercise periodic breathing all have prognostic value in CHF (Frankenstein et al., 2008; Giannoni et al., 2009; Ribeiro et al., 2006). We have previously shown that inspiratory muscle training markedly improves inspiratory muscle strength and also reduces exercise-induced ventilatory oscillations in patients with CHF and IMW (Dall'Ago et al., 2006; Winkelmann et al., 2009). The associations found in the present study raise the hypothesis that inspiratory muscle training may also affect chemoreflex responsiveness, with possible impact on survival. Therefore, future studies should be conducted to test this hypothesis.

5. Conclusion

Our findings indicate that IMW is linked to increased peripheral chemoreflex responsiveness and augmented exercise ventilatory oscillation in patients with CHF.

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CONCLUSÕES

1. A vasoconstrição periférica induzida pelo trabalho muscular inspiratório fatigante encontra-se atenuada em indivíduos treinados aerobicamente, sugerindo que o exercício aeróbico regular atenua o metaborreflexo inspiratório.

2. A fraqueza muscular inspiratória está associada com aumento da resposta do quimiorreflexo periférico em pacientes com insuficiência cardíaca crônica.

ANEXOS

Formação complementar durante o doutorado

Artigos publicados

Artigos em preparo

Seminários

Revisão de artigos

Vivência em projetos de pesquisa

Reabilitação

Cursos

Habilidades técnicas

Publicações em anais de eventos

Artigos publicados

1. Callegaro CC, Martinez D, Ribeiro P, Brod M, Ribeiro JP. Augmented peripheral chemoreflex in patients with heart failure and inspiratory muscle weakness. *Respiratory Physiology & Neurobiology*. 2010, 171: 31-35.

Artigos em preparo

1. Callegaro CC, Ribeiro JP, Tan CO, Taylor JA. Attenuated respiratory muscle metaboreflex in endurance-trained individuals. *J Appl Physiol*.
2. Callegaro CC & Taylor JA. Age-related effects of vagotonic atropine on cardiovagal baroreflex gain. *Neurobiology of aging.*

Seminários

1. Journal Club no Cardiovascular Research Laboratory, Spaulding Rehabilitation Hospital, associado à Harvard Medical School. Seminário sobre fisiologia e reabilitação cardiovascular coordenado semanalmente pelo Prof. Dr. J Andrew Taylor.
2. Journal Club no Beth Israel Deaconess Division of Pulmonary and Critical Care Medicine associado à Harvard Medical School. Seminário sobre fisiologia respiratória como enfoque no estudo dos efeitos autonômicos e cardiovasculares da hipóxia coordenado semanalmente pelos professores Prof. Dr. J Andrew Taylor and Prof. Dr. Wood Weiss.

3. Seminário do Department of Physical Medicine and Rehabilitation do Spaulding Rehabilitation Hospital, realizado mensalmente com enfoque em reabilitação.

Revisão de artigos

Revisão de artigos para *Circulation, Circulation Research, Hypertension, Journal Physiology e Journal Applied Physiology* sob supervisão do Prof. Dr. J Andrew Taylor.

Vivência em projetos de pesquisa

1. Vagotonic effects of atropine on baroreflex sensitivity in young and older subjects.

2. Vagolitic effects of atropine on baroreflex sensitivity in young subjects.

3. Aerobic exercise training for older healthy subjects.

4. Musculoskeletal and cardiorespiratory effects of hybrid-FES row training in spinal cord injury.

5. Physiological investigation of yogic-derived slow breathing.

6. Associação entre o polimorfismo dos receptores beta1-adrenérgicos e a resposta cardiorrespiratória ao exercício em pacientes com insuficiência cardíaca congestiva.

Reabilitação

1. Integrante do programa de exercícios para pessoas com limitações (ExPD). Programa de treinamento de remo associado com estimulação elétrica funcional em pacientes com lesão medular completa ou incompleta.

2. Participante do programa de treinamento de remo na água associado à estimulação elétrica funcional para pacientes com lesão medular completa.

3. Demonstração prática do programa de remo associado à estimulação elétrica funcional no solo para a Comunidade de Remo de Boston (Rowing Community).

Cursos

1. Statistics for clinical studies realizado na Harvard Medical School.
2. Academic presentation and pronunciation realizado na Park Street Church.
3. Cientific Writing realizado na Park Street Church.

Habilidades técnicas

Estimativa do débito cardíaco por reinalação de CO_2; avaliação da sensibilidade quimiorreflexa; avaliação da função endotelial; determinação do fluxo sanguíneo poplíteo e cerebral por *Doppler*;

avaliação e análise da sensibilidade barorreflexa: técnica de Oxford modificada, neck chamber e manobra de Valsalva.

Publicações em anais de eventos

1. Ribeiro JP, Callegaro CC, Schneider FL, Simões EN, Silveira JV, Marini L, Martinez D. Exaggerated peripheral chemoreflex response in heart failure with inspiratory muscle weakness. In: EuroPRevent 2008 Congress, 2008, Paris. **European Journal of Cardiovascular Prevention & Rehabilitation**, 2008. v.15 Suppl. p.S113.

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