Universidade do Estado do Rio de Janeiro

Centro Biomédico

Faculdade de Ciências Médicas

Renata Rodrigues Teixeira de Castro

Variabilidade ventilatória durante exercício dinâmico em indivíduos saudáveis e com insuficiência cardíaca

Rio de Janeiro

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Tese apresentada, como requisito parcial para obtenção do título de Doutor, ao Programa de Pós-graduação em Fisiopatologia Clínica e Experimental, da Universidade do Estado do Rio de Janeiro. Área de concentração: Fisiopatologia.

Orientador: Prof. Dr. Antonio Claudio Lucas da Nóbrega

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Renata Rodrigues Teixeira de Castro

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DEDICATÓRIA

À minha família, pelo apoio incondicional, em todos os momentos da minha vida.

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Ao Prof. Antonio Claudio Lucas da Nóbrega, muito mais que um orientador, um amigo e exemplo profissional, científico e pessoal.

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Aos voluntários que participaram dos projetos da tese.

Se fui capaz de enxergar mais longe, é porque estava apoiado sobre o ombro de gigantes.

Isaac Newton

RESUMO

CASTRO, Renata Rodrigues Teixeira de. *Variabilidade ventilatória durante exercício dinâmico em indivíduos saudáveis e com insuficiência cardíaca.* 2010. 110 f. Tese (Doutorado em Fisiopatologia Clínica e Experimental) – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, 2010.

A presença de ventilação periódica durante o exercício confere pior prognóstico a pacientes com insuficiência cardíaca. Existem divergências quanto aos critérios para identificação deste fenômeno. Além disso, a interpretação dicotômica (presença ou ausência) quanto a este fenômeno dificulta a estratificação de risco mais detalhada dos pacientes com insuficiência cardíaca. Desta forma, esta tese avalia a utilização de técnicas estabelecidas para análise de variabilidade de sinais para quantificar as oscilações ventilatórias que ocorrem durante o teste cardiopulmonar de exercício, em indivíduos saudáveis, atletas e com insuficiência cardíaca. Um protocolo mais curto para realização de teste cardiopulmonar de exercício em cicloergômetro de braço foi proposto e validado. Tal protocolo foi utilizado em estudo posterior, onde se comprovou que, apesar dos tempos respiratórios não serem influenciados pelo tipo de exercício realizado, a variabilidade ventilatória é maior durante a realização de exercício dinâmico com membros superiores do que com membros inferiores. A capacidade aeróbica de indivíduos sadios também influencia a variabilidade ventilatória durante o teste cardiopulmonar de exercício. Isto foi comprovado pela menor variabilidade ventilatória no domínio do tempo em atletas do que sedentários durante exercício. A análise destes voluntários com o método da análise dos componentes principais revelou que em atletas a variabilidade do volume corrente é a principal responsável pela variabilidade da ventilação-minuto durante o exercício, ao passo que em sedentários a variabilidade da freqüência respiratória apresenta-se como principal responsável por tais variações. Em estudo randomizado e controlado comprovamos que, mesmo indivíduos sadios apresentam redução da variabilidade ventilatória ao exercício após 12 semanas de treinamento físico. Comprovamos que a reabilitação cardíaca reverteu a ocorrência de ventilação periódica em um paciente com insuficiência cardíaca e, finalmente, encontramos que a variabilidade ventilatória correlaciona-se inversamente com a fração de ejeção ventricular esquerda em pacientes com insuficiência cardíaca. Estudos futuros deverão analisar o poder prognóstico da variabilidade ventilatória nestes pacientes.

Palavras-chave: Insuficiência cardíaca. Exercício. Ventilação periódica. Variabilidade. Atletas. Treinamento físico.

ABSTRACT

Exercise periodic breathing confers a bad prognosis in patients with heart failure. There is no agreement among proposed criteria to diagnose exercise periodic breathing. The dichotomic interpretation (presence or absence) when diagnosing this phenomenon impairs a more detailed risk stratification in heart failure. Thus, this thesis evaluates the use of established signal variability techniques to quantify ventilatory oscillations during cardiopulmonary exercise test, in healthy individuals, athletes and patients with heart failure. A short protocol used to perform cardiopulmonary exercise test in arm crank was proposes and validated. This protocol was used in the next study, which found that, although timing of breathing was not altered by exercise type, ventilatory variability was greater during arm dynamic exercise when compared to leg exercise. Aerobic capacity of healthy individuals also influences ventilatory variability during cardiopulmonary exercise test. This was proven by the lower time-domain ventilatory variability in athletes when compared to sedentary individuals. The evaluation of these individuals with principal components analysis showed that tidal volume variability is the principal component o minute-ventilation variability in athletes, whilst in sedentary men, respiratory frequency variability is the responsible for minute-ventilation variability. In a randomized controlled study we have found that even healthy individuals reduce their exercise ventilatory variability after 12 weeks exercise training. We have shown that cardiac rehabilitation reverted exercise periodical breathing in a patient with heart failure and, finally, found that exercise ventilatory variability inversely correlates to left ventricle ejection fraction in patients with heart failure. Future studies should evaluate the prognostic value of ventilatory variability in these patients.

Key words: Heart failure. Exercise. Periodical breathing. Variability. Athletes. Exercise training.

LISTA DE ABREVIATURAS E SIGLAS

ATHR-	*Anaerobic threshold heart rate*
CO_2-	Dióxido de carbono/ *Carbon dioxide*
FR-	Freqüência respiratória
LA-	Limiar anaeróbico
O_2-	Oxigênio/ *Oxygen*
PCA-	Análise dos componentes principais
RMSSD-	Raiz quadrada das médias das diferenças entre intervalos consecutivos/ *root mean square of successive differences*
RMSSD/n-	*Root mean square of successive differences normalized by the number of breaths*
RQ-	*Respiratory quotient*
RR-	*Respiratory rate*
SD-	Desvio padrão/ *Standard deviation*
SD/n-	*Standard deviation normalized by the number of breaths*
TCPE-	Teste cardiopulmonar de exercício
Te-	Tempo expiratório/ *Expiratory time*
Ti-	Tempo inspiratório/ *Inspiratory time*
Ttot-	Tempo total do ciclo respiratório/ t*otal respiratory time*
VCO_2-	Produção de dióxido de carbono/ Carbon dioxide output
V_E-	Ventilação-minuto/ *minute-ventilation*
VE/VCO_2-	Equivalente respiratório para o dióxido de carbono/ *respiratory equivalent for carbon dioxide*
VE/VO_2-	Equivalente respiratório para o oxigênio/ *respiratory equivalent for oxygen*
VO_2-	Consumo de oxigênio/ *Oxygen uptake*
Vt-	Volume corrente ou tidal/ *tidal volume*

SUMÁRIO

INTRODUÇÃO

Este documento apresenta e discute diferentes aspectos da variabilidade ventilatória durante a realização de exercício físico dinâmico em indivíduos saudáveis e pacientes com insuficiência cardíaca. Todos os resultados aqui apresentados são fruto de subprojetos que compõem meu projeto de doutorado em Fisiopatologia Clínica e Experimental da Universidade do Estado do Rio de Janeiro. Durante o período em que cursei o programa de doutorado alguns destes subprojetos foram publicados ou aceitos para publicação em periódicos internacionais indexados. Assim, optei por apresentar cada um destes no formato em que foram apreciados, e aceitos, para publicação. Acredito que a apresentação no presente formato facilitará o entendimento do conteúdo. Vale ressaltar que os artigos serão apresentados em seu formato original, ou seja, formatados de acordo com as regras específicas dos periódicos aos quais foram submetidos.

Os artigos publicados/ submetidos durante o período de doutorado e aqui apresentados na íntegra são:

1. Castro RRT, Pedrosa S, Chabalgoity F, Sousa EB, Nóbrega ACL. The influence of a fast ramp rate on peak cardiopulmonary parameters during arm crank ergometry. Clin Physiol Func Imag 2010; 30: 420-5. Fator de impacto: 1,183

2. Castro RRT, Pedrosa S, Nobrega ACL. Different ventilatory responses to progressive maximal exercise test performed with either arms or legs. Submetido para Respiratory Medicine. Fator de impacto: 2,331

3. Castro RRT, Magini M, Pedrosa S, Salles ARK, Nobrega ACL. Principal components analysis to evaluate ventilatory variability: comparison of athletes and sedentary men. Aceito para publicação na Medical & Biological Engineering & Computing. Fator de impacto: 1,691

4. Castro RRT, Pedrosa S, Salles ARK, Nobrega ACL.Time-domain ventilatory variability is higher in sedentary than athlete men during a maximal exercise test. Submetido para European Respiratory Journal. Fator de impacto: 5,545.

5. Castro RRT, Salles ARK, Nobrega ACL. Physical training reduces time-domain ventilatory variability during exercise in healthy individuals: a randomized trial. Submetido para European Journal of Cardiovascular Prevention and Rehabilitation. Fator de impacto: 2,361.

6. Castro RRT, Antunes-Correa LM, Ueno LM, Rondon MUPB, Nóbrega ACL. Reversal of periodic breathing after aerobic training in heart failure. Eur Resp J 2010; 35: 1409-11. Fator de impacto: 5,545.

7. Castro RRT, Antunes-Correa LM, Ueno LM, Rondon MUPB, Nóbrega ACL. Ventilation variabillity inversely correlates to ejection fraction in heart failure. Eur Resp J 2010; 36: 1-2. Fator de impacto: 5,545.

A homeostase pode ser considerada o cerne do estudo da fisiologia humana (1). Sua manutenção decorre de um processo contínuo, dependente de diferentes mecanismos de *feedback* que operam visando manter parâmetros biológicos dentro de determinados valores de normalidade. Assim, praticamente todos os parâmetros biofísicos exibem certa variabilidade temporal e, em alguns casos, a análise desta variabilidade pode ser útil para o diagnóstico e prognóstico de doenças.

O interesse a respeito da variabilidade da ventilação durante a realização de exercício físico ganhou mais atenção nas últimas décadas, desde os primeiros relatos que descreveram o fenômeno (2) até mais recentemente, quando foi confirmado o forte poder prognóstico deste fenômeno em pacientes com insuficiência cardíaca (3-5).

Nas próximas sessões serão apresentados e discutidos diferentes aspectos da variabilidade da ventilação durante o exercício físico dinâmico, incluindo não apenas seu comportamento fisiológico, mas também em pacientes com insuficiência cardíaca.

1 **REVISÃO DA LITERATURA**

1.1 **Fisiologia respiratória durante o exercício**

Durante o exercício ocorrem diferentes respostas fisiológicas que visam atender à demanda metabólica dos músculos em atividade. Destacam-se, entre estas respostas, o aumento da atividade dos sistemas cardiovascular e respiratório, visando, em última análise, atender à demanda metabólica celular. Nesta sessão revisaremos aspectos básicos da fisiologia respiratória durante o exercício, que servirão de embasamento teórico para a discussão de outros temas desta tese.

Antes de descrevermos especificamente as respostas ventilatórias fisiológicas ao exercício, torna-se necessária a definição de alguns termos, conforme abaixo:

Volume corrente ou tidal (Vt): Volume de ar inspirado ou expirado durante cada ciclo respiratório

Tempo inspiratório: Duração da fase inspiratória do ciclo respiratório

Tempo expiratório: Duração da fase expiratória do ciclo respiratório

Tempo total do ciclo respiratório (Ttot): Duração do ciclo respiratório, ou seja, soma dos tempos ins- e expiratório (figura 1).

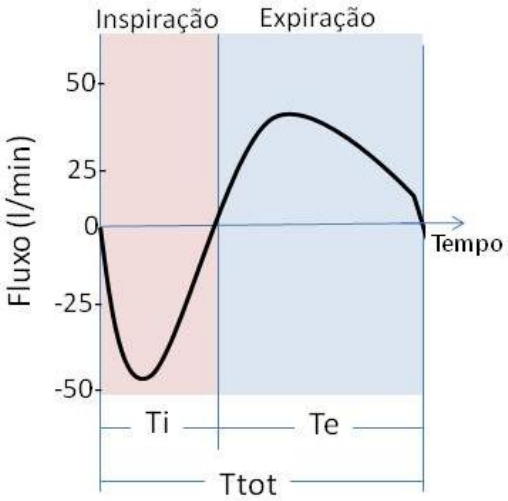

Figura 1 - Tempos respiratórios

Ti: tempo inspiratório; Te: tempo expiratório; Ttot: Tempo total do ciclo respiratório

Freqüência respiratória (FR): Número de respirações que ocorrem durante um minuto. Ao considerar valor fixo de Ttot pode-se aferir que a FR é o inverso do Ttot.

Ventilação-minuto (VE): Volume de ar que é inspirado a cada minuto.

Assim, se considerarmos valores fixos de FR e Vt, podemos inferir que:

Equação 1: VE= Vt x FR

Um dos principais estímulos à ventilação durante o exercício é a produção de dióxido de carbono (CO_2) resultante da respiração celular. A baixa concentração de CO_2 capilar permitirá a difusão de CO_2 das células para o sangue que perfunde os músculos em atividade. Para que isso seja possível, é mandatório que o sangue que chega aos pulmões seja arterializado, ou seja, permita a difusão de CO_2 para os alvéolos e receba oxigênio (O_2) dos mesmos. A V_E aumenta de forma adequada a permitir a remoção do CO_2 a nível alveolar. Tal afirmativa é verdadeira em intensidades de exercício abaixo do limiar anaeróbico. Em intensidades acima do limiar anaeróbico, a acidose torna-se um potente estímulo à ventilação e, nesta situação, a ventilação aumenta além dos valores necessários para permitir a eliminação do CO_2 arterial (6).

Conforme já descrito, V_E é produto da interação entre Vt e FR. Conseqüentemente, alterações nos valores de Vt e FR podem contribuir de formas diferentes para a resultante VE. Assim, sabe-se que em exercícios de intensidade leve a moderada, o aumento de Vt é o principal responsável pelo aumento de VE, ao passo que durante exercícios mais intensos, o aumento da FR torna-se essencial para o aumento de V_E (7).

O teste cardiopulmonar de exercício (TCPE) representa ferramenta essencial para o entendimento da fisiologia respiratória e detecção de anormalidades ventilatórias durante o exercício, entre outras aplicabilidades. Em linhas gerais, durante a realização deste exame, um indivíduo é estimulado a realizar exercício dinâmico, com aumento progressivo de intensidade, desde o repouso até seu esforço máximo. Durante o exame, são registrados, além de sinais clínicos e eletrocardiográficos e da medida intermitente da pressão arterial, consumo de O_2, produção de CO_2, Vt, Ttot. Estes registros permitem o cálculo de outras variáveis, tais como VE, FR e os equivalentes respiratórios para O_2 (VE/VO_2) e CO_2 (VE/VCO_2). Descreveremos a seguir o comportamento fisiológico destas variáveis durante teste cardiopulmonar de exercício seguindo protocolo individualizado de rampa, caracterizado por aumentos graduais e progressivos da intensidade do exercício.

1.1.1 Ventilação pulmonar

Durante TCPE a V_E aumenta paralelamente ao aumento do consumo de oxigênio (VO_2), da produção de dióxido de carbono (VCO_2) e da carga de trabalho até que seja alcançado o limiar ventilatório, que ocorre em nível de esforço correspondente à cerca de 50-70% do VO_2 máximo (VO_2 max). A partir deste ponto, o incremento da V_E torna-se mais acelerado do que o incremento do VO_2, mas ainda proporcional ao incremento do VCO_2 (8). Discutiremos o fenômeno do limiar ventilatório mais adiante desta sessão.

1.1.2 VO_2 de pico e VO_2 máximo

O VO_2 max é uma das medidas mais importantes derivadas do TCPE, pois define os limites máximos do sistema cardiopulmonar. Considera-se que o TCPE foi máximo quando este permitiu identificar o VO_2 max. Por definição, este é identificado quando ocorre um platô na curva de VO_2 (ausência de aumento na medida do VO_2 apesar de aumento contínuo na carga de trabalho- Figura 2). Taylor e colaboradores (9) definiram o platô como a incapacidade de aumentar o VO_2 em mais de 150ml/min, ou 2,1 ml/kg/min, apesar de um aumento na carga de trabalho. Freqüentemente não é possível identificar um platô no VO_2, tendo sido inclusive questionada a sua real existência (10). Por esta razão, quando não se alcança o platô de VO_2, o VO_2 alcançado no ponto máximo do esforço é denominado VO_2 de pico e não VO_2 máximo.

Um estudo recente (11) que acompanhou mais de 15.000 homens por um período médio de sete anos, comprovou que o VO_2 de pico é um forte preditor de mortalidade global em brancos e negros. A mortalidade é inversamente proporcional ao VO_2 de pico, com redução de 13% na mortalidade para cada aumento de 3,5 mL/kg/min no VO_2 pico.

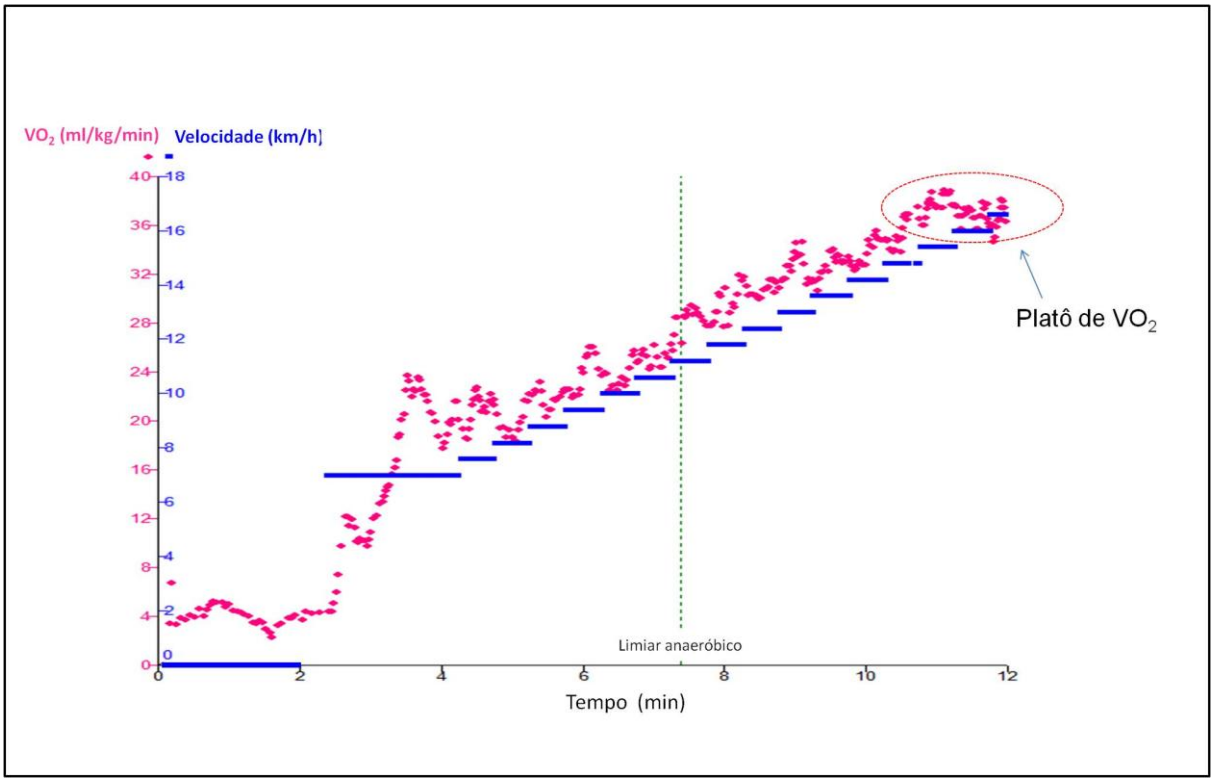

Figura 2- Platô do consumo de oxigênio (VO_2)
Exemplo de teste cardiopulmonar de exercício, seguindo protocolo individualizado de rampa. O platô de VO_2 fica evidente pela ausência do aumento na medida do VO_2 (círculos cor-de-rosa) apesar do aumento contínuo na carga de trabalho (linhas azuis).

1.1.3 VCO_2

A produção de CO_2 durante o exercício físico é derivada de duas fontes: metabolismo oxidativo e tamponamento do ácido lático que ocorre em esforços mais intensos. Em esforços abaixo do limiar ventilatório o VCO_2 apresenta aumento paralelo ao aumento do VO_2. Quando a intensidade do esforço ultrapassa o limiar ventilatório, ocorre um acúmulo sangüíneo de ácido lático. Tal fato tornaria o pH sanguíneo mais ácido, mas os mecanismos de controle desencadeiam um aumento na taxa de incremento da V_E e do VCO_2 a partir deste ponto, mantendo o pH relativamente constante. Em esforços ainda mais intensos, pode ocorrer acidose, deflagrando hiperventilação, ou seja, aumento do fluxo expiratório de CO_2 em intensidade maior do que a síntese, levando à hipocapnia.

1.1.4 Equivalentes ventilatórios para oxigênio e dióxido de carbono

O V_E/VO_2 representa um índice da eficiência ventilatória, pois reflete a ventilação necessária para a obtenção de um determinado aporte de oxigênio. Pacientes com doenças pulmonares caracterizadas por aumento do espaço morto (12), e pacientes com insuficiência cardíaca (13) apresentam uma ineficiência ventilatória que se expressa por aumento da relação V_E/VO_2.

O V_E/VCO_2 representa a ventilação necessária para a eliminação de um determinado fluxo de dióxido de carbono. O V_E/VCO_2 também representa fisiologicamente o espaço morto pulmonar e a relação ventilação-perfusão, uma vez que a pressão parcial arterial de CO_2 é uma variável que depende primariamente da ventilação alveolar.

1.1.5 Limiar ventilatório

O nível de esforço físico a partir do qual ocorre acúmulo sangüíneo de lactato é denominado de limiar ventilatório, ou anaeróbico. Acima do limiar ventilatório, o acúmulo de ácido lático acarreta uma tendência para o aumento da pressão parcial venosa de CO_2, o que resulta em aumento do incremento de VCO_2 e de V_E, mantendo, desta forma, a pressão parcial arterial de CO_2 constante. Como o VO_2 permanece com aumento linear (proporcional ao nível de esforço), enquanto a taxa de incremento da V_E aumenta, temos uma maior elevação do V_E/VO_2 em relação ao V_E/VCO_2 e aumento também da fração expirada de oxigênio. Esse fenômeno corresponde ao limiar ventilatório I. Com a continuidade do esforço, a V_E aumenta mais depressa que a produção de CO_2, o que resulta em maior aceleração do V_E/VCO_2, indicando o chamado limiar ventilatório II (14).

O limiar ventilatório I (algumas vezes chamado de limiar aeróbico) não define o início da anaerobiose durante o exercício, mas o ponto a partir do qual a capacidade de remoção do lactato do organismo é ultrapassada pela taxa de formação deste composto. Apesar do mecanismo exato responsável por este fenômeno ainda ser controverso, as conseqüências são, além do acúmulo de lactato, acidose muscular com dor local em queimação e alterações respiratórias, como aumento mais acentuado da eliminação de CO_2 e da V_E (14).

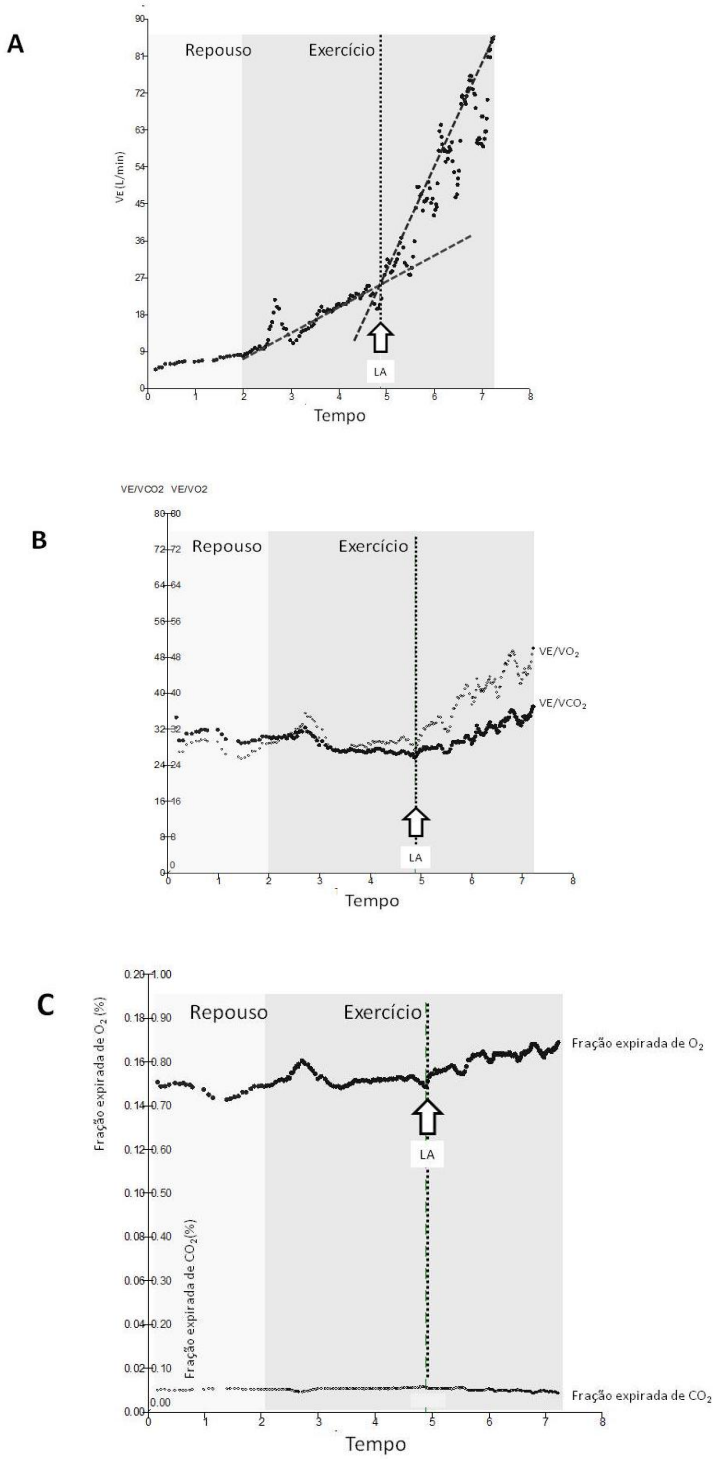

Figura 3 - Identificação do limiar anaeróbico
As setas indicam o limiar ventilatório I (LA), de acordo com cada critério: A) ponto de exponenciação da ventilação; B) aumento do Ve/VO_2 sem aumento concomitante do Ve/VCO_2; C) aumento da fração expirada de oxigênio.

A identificação do limiar ventilatório I é tema freqüente de discussão entre especialistas. Tal identificação pode ser feita através da dosagem direta de lactato sangüíneo ou, não invasivamente, através do TCPE. No TCPE, o aumento exponencial da V_E em relação ao VO_2 ou o aumento da fração expirada de oxigênio identificam o limiar ventilatório. Além destes, o aumento do V_E/VO_2 e a modificação da inclinação da curva que relaciona VCO_2 e VO_2 também são utilizados na identificação do limiar ventilatório (Figura 3).

1.2 **Controle da respiração**

1.2.1 Controle neural da respiração

Os ciclos respiratórios passivos envolvem contrações e relaxamentos rítmicos e sucessivos da musculatura inspiratória (diafragma e músculos intercostais externos). Na respiração ativa, a musculatura inspiratória acessória (músculos Esternocleidomastóideos e Escalenos) e a musculatura expiratória (músculos Retos abdominais, Transversos abdominais, Oblíquos internos e externos e Intercostais internos) também estão envolvidas (Figura 4).

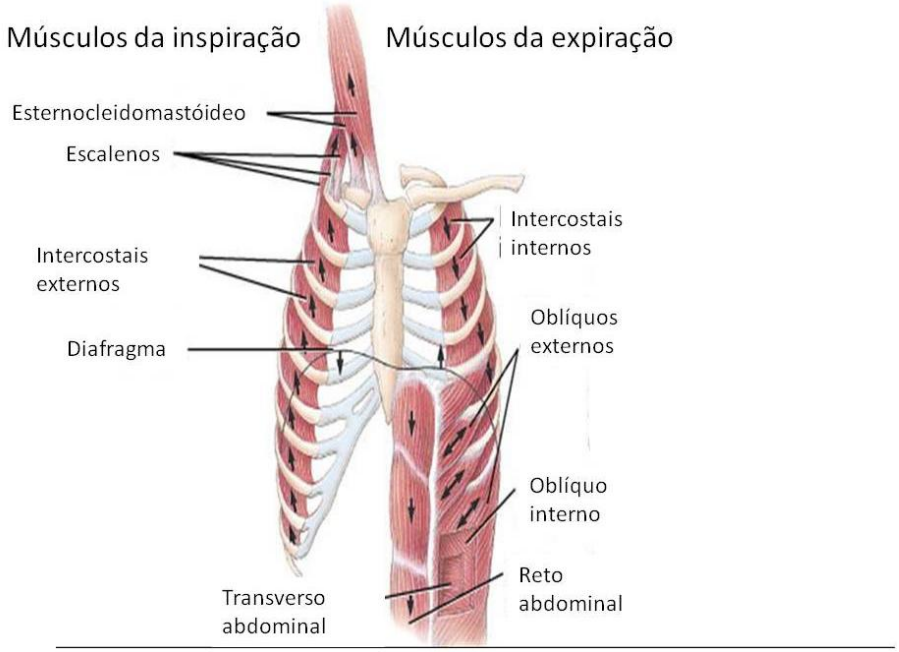

Figura 4- Músculos envolvidos na respiração
Adaptado de http://faculty.ccri.edu/kamontgomery/anatomy%20respiration.htm

1.2.1.1 Centro respiratório

O centro respiratório é composto por vários grupos de neurônios localizados bilateralmente na medula oblongata e na ponte. Tais neurônios agrupam-se e compõem as três divisões do centro respiratório: grupo respiratório dorsal (relacionado principalmente à inspiração), grupo respiratório ventral (relacionado principalmente à expiração) e centro pneumotáxico. O centro pneumotáxico localiza-se na porção superior da ponte e participa no controle da freqüência e do padrão respiratório (Figura 5).

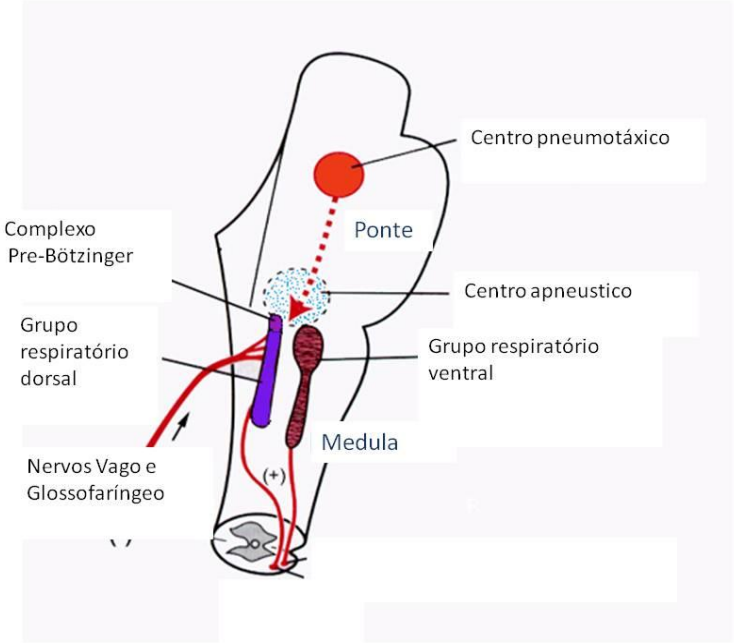

Figura 5 - Organização do centro respiratório
Adaptado de http://www.colorado.edu/intphys/Class/IPHY3430-200/015breathing.htm

A maior parte dos neurônios do grupo respiratório dorsal localiza-se no núcleo do trato solitário, que é a terminação sensorial dos nervos Glossofaríngeo e Vago. Tais nervos transmitem, ao centro respiratório, sinais oriundos dos quimiorreceptores periféricos, barorreceptores e receptores pulmonares, conforme será apresentado a seguir (15).

Os neurônios do grupo respiratório dorsal disparam potenciais de ação inspiratórios repetidamente. Os exatos mecanismos deste fenômeno permanecem desconhecidos (16). Os sinais nervosos transmitidos à musculatura inspiratória começam apresentam aumento progressivo de sua intensidade, cessando

abruptamente ao atingir seu ápice. Até que estes neurônios disparem novamente, acontece a expiração. Este sinal inspiratório em “rampa” permite a expansão gradual dos pulmões, evitando espasmos na musculatura respiratória.

O centro pneumotáxico transmite sinais para o grupo respiratório dorsal, interrompendo a inspiração e assim controlando a duração do ciclo respiratório. Dois mecanismos são propostos na regulação das fases inspiratória e expiratória do ciclo respiratório (17). Um destes mecanismos envolve o reflexo de Hering-Breuer (18). Tal reflexo caracteriza-se pelo *feedback* aferente vagal oriundo de receptores de estiramento pulmonar. A ausência do reflexo de Hering-Breuer, conseqüente à vagotomia, implica em longos períodos inspiratórios, aumento da amplitude dos impulsos nervosos do grupo respiratório dorsal e menor freqüência respiratória (18, 19).

Apesar do reflexo de Hering-Breuer ser considerado o principal responsável pela determinação da duração do tempo respiratório e, conseqüentemente, pela relação entre as durações dos tempos inspiratório e expiratório, a Ponte também parece exercer algum papel na transição inspiração-expiração, ao menos quando o reflexo de Hering-Breuer não está intacto (17, 20).

1.2.1.2 Controle voluntário da respiração

O controle voluntário da respiração não parece ser mediado através do centro respiratório medular. Os neurônios que controlam a respiração voluntariamente passam diretamente do córtex cerebral pelo trato córtico-espinhal até os neurônios motores da musculatura respiratória (21-23).

1.2.1.3 Efeitos da contração muscular sobre a respiração

Existem evidências de que a contração muscular interfere na respiração (24). Durante contração muscular passiva ocorre aumento da ventilação (25). Além disso, já foi demonstrado que a transecção medular parcial atenua a resposta de hiperpnéia no início do exercício (26). Entretanto, os efeitos metabólicos da contração muscular em intensidades e durações mais elevadas (alterações nas concentrações sangüíneas de dióxido de carbono, hidrogênio e oxigênio) são

estímulos muito mais potentes para a respiração do que a contração muscular em si, conforme já apresentado.

1.2.2 Controle químico da respiração

Os principais objetivos da respiração são manter concentrações teciduais adequadas de oxigênio, dióxido de carbono e hidrogênio. A área quimio-sensível do centro respiratório, localizada na área ventral da medula, é muito sensível às alterações nas concentrações de hidrogênio e gás carbônico. Desta forma, aumentos nas concentrações de dióxido de carbono ou hidrogênio sangüíneos atuam diretamente sobre o tronco cerebral, causando aumentos na freqüência e intensidade dos impulsos nervosos à musculatura inspiratória e expiratória.

A barreira hemoto-encefálica é pouco permeável ao hidrogênio. Assim, apesar da área quimio-sensível do centro respiratório ser facilmente excitada pelo excesso de íons hidrogênio, os aumentos de sua concentração na corrente sangüínea acabam gerando menos efeito sobre o controle respiratório que alterações nas concentrações sangüíneas de gás carbônico. Na verdade, o dióxido de carbono que ultrapassou a barreira hemato-encefálica reage com a água tecidual, gerando ácido carbônico. Este rapidamente dissocia-se em hidrogênio e bicarbonato. O hidrogênio resultante desta reação ativará os neurônios da área quimio-sensível do centro respiratório (27).

O aumento da concentração sangüínea de dióxido de carbono é um potente estímulo agudo à respiração. Este efeito não é tão potente quando tais concentrações estão cronicamente elevadas. Conforme já apresentado, aumentos nas concentrações sanguíneas de dióxido de carbono resultam em aumentos na concentração sangüínea de hidrogênio. A resposta renal a este aumento é uma maior produção de bicarbonato, que tampona os íons hidrogênio. Isto ocorre não só a nível sistêmico, mas também após o bicarbonato se difundir através da barreira hemato-encefálica e se combinar diretamente com os íons hidrogênio próximos ao centro respiratório. Desta forma, a concentração de hidrogênio próxima à área quimio-sensível também diminuiu, reduzindo o estímulo respiratório ao aumento crônico de dióxido de carbono local (27, 28).

Quando a concentração arterial de oxigênio cai abaixo de 70 mmHg, ativam-se os quimiorreceptores periféricos. A maioria destes quimiorreceptores periféricos

está localizada nos corpos carotídeos (29, 30). Além destes, outros estão localizados na crossa da aorta e outras artérias torácicas e abdominais. Fibras aferentes dos quimiorreceptores periféricos passam pelo nervo Glossofaríngeo (quimiorreceptores localizados nos corpos carotídeos) ou pelo nervo Vago (quimiorreceptores localizados na crossa da aorta) e seguem para a área respiratória dorsal da medula (31).

1.2.3 Temperatura

Exceto durante exercícios prolongados, a temperatura central e muscular têm poucos efeitos sobre o controle ventilatório em humanos (24).

1.3 **Alterações respiratórias na insuficiência cardíaca**

A insuficiência cardíaca é muito prevalente no mundo ocidental. Nos Estados Unidos da América, em 2005, existiam mais de cinco milhões de pacientes com insuficiência cardíaca, sendo diagnosticados 550.000 casos novos por ano. A prevalência desta doença implica na realização de 12 a 15 milhões de consultas médicas e 6,5 milhões de diárias hospitalares por ano, somando gastos anuais de US$ 20 bilhões. No ano 2000, foram realizadas 398.000 internações por insuficiência cardíaca no Brasil. A insuficiência cardíaca representa a principal causa de internação de pacientes idosos pelo Sistema Único de Saúde brasileiro (32).

A insuficiência cardíaca caracteriza-se, de forma simplificada, pela incapacidade do coração em bombear sangue de forma a atender adequadamente às demandas metabólicas teciduais. Entretanto, atualmente sabe-se que se trata de doença sistêmica.

O fato de pacientes com insuficiência cardíaca raramente evoluírem com hipoxemia contribuiu para que, durante muitos anos, a importância da avaliação da função pulmonar destes pacientes fosse negligenciada. Entretanto, atualmente sabe-se que, na insuficiência cardíaca, a disfunção pulmonar é freqüente (33) e sua gravidade correlaciona-se com a severidade da disfunção ventricular (34, 35). Independente da presença de comorbidades que afetem diretamente a função pulmonar, como o tabagismo, pacientes com insuficiência cardíaca exibem testes de função pulmonar em repouso com padrão fisiológico ou compatível com doença restritiva (33).

Diferentes mecanismos são propostos e, na verdade, parecem atuar em conjunto, para a ocorrência de disfunção respiratória em pacientes com insuficiência cardíaca. Apesar de não estar diretamente relacionada à função pulmonar, a presença de anemia secundária à insuficiência cardíaca é um fator que contribui para a o desconforto respiratório destes pacientes (36).

No que tange à disfunção pulmonar propriamente dita, Agostoni e colaboradores (37) avaliaram 80 pacientes com insuficiência cardíaca em classes funcionais II e III da Associação Nova-iorquina do coração (NYHA) e concluíram que a cardiomegalia reduz o volume alveolar, gerando restrição respiratória e conseqüentes efeitos deletérios sobre a difusão de CO_2. Os efeitos mecânicos da cardiomegalia sobre a função pulmonar seriam ainda mais evidentes de acordo com a posição adotada

pelo pacientes. Mais especificamente, foi demonstrado que quanto maiores as dimensões cardíacas, maiores as diferenças entre a função pulmonar avaliada com paciente em posição sentada ou em decúbito lateral (38). Segundo tal estudo (38), durante decúbito lateral (direito ou esquerdo) ocorre obstrução de vias aéreas e prejuízo da difusão de CO_2, por compressão mecânica do coração aumentado de tamanho sobre as vias aéreas.

Um estudo recém publicado sugere que o volume cardíaco influencia o padrão respiratório durante o exercício (39). Olson e colaboradores (39) avaliaram 37 pacientes com insuficiência cardíaca e encontraram menores volumes correntes no pico do exercício naqueles pacientes com maiores volumes cardíacos. Ou seja, o aumento do espaço na cavidade torácica ocupado pelo coração, restringiria os volumes pulmonares e teria influência sobre o padrão ventilatório durante o exercício máximo.

A presença de derrame pleural secundário à disfunção ventricular também pode ser causa de piora da função respiratória (40), reduzindo a capacidade vital forçada, capacidade pulmonar total e a capacidade de difusão de pacientes com insuficiência cardíaca. Finalmente, mas não menos importante, o aumento de líquido intersticial pulmonar, resultante da maior pressão capilar pulmonar na insuficiência cardíaca, também prejudica a função pulmonar destes pacientes. Mais especificamente, já foi comprovada a melhora da função pulmonar, com melhora da capacidade vital, volume expiratório forçado e ventilação voluntária máxima, em pacientes submetidos à ultra-filtração extracorpórea (41).

A troca gasosa, representada pela difusão alvéolo-capilar, também está alterada na insuficiência cardíaca (42, 43). As alterações anatômicas da membrana alvéolo-capilar nestes casos incluem redução do número de unidades alvéolo-capilares, fibrose intersticial, trombose local e aumento da celularidade (44). Aumentos agudos e transitórios na pressão da microvasculatura pulmonar secundários à disfunção ventricular esquerda seriam os responsáveis pela ruptura da barreira alvéolo-capilar, com conseqüente liberação de proteína surfactante tipo B na corrente sanguínea (45, 46). De Pasquale e colaboradores (47) comprovaram que os níveis circulantes da proteína surfactante tipo B correlacionam-se com a gravidade do quadro de insuficiência cardíaca. Mais recentemente, comprovou-se que os níveis séricos desta proteína estão inversamente correlacionados com a capacidade de difusão da membrana alvéolo-capilar em pacientes com insuficiência cardíaca (48).

Apesar de, conforme aqui apresentado, muitos pacientes com insuficiência cardíaca já apresentarem alterações respiratórias em repouso, nenhuma condição é mais propícia para o estudo da função pulmonar destes pacientes do que o exercício físico (34). As maiores demandas metabólicas durante o exercício maximizam as alterações pulmonares, facilitando sua detecção mesmo em indivíduos que porventura apresentem testes de função pulmonar normais em repouso. O TCPE em pacientes com insuficiência cardíaca caracteriza-se, em linhas gerais, por baixo consumo de oxigênio (VO_2) no pico do exercício e hiperventilação. Ou seja, para uma determinada carga, pacientes com insuficiência cardíaca exibem maior ventilação quando comparados a indivíduos sadios, associada ao aumento progressivo da freqüência respiratória e menor volume corrente (33). A hiperventilação na insuficiência cardíaca é multifatorial, incluindo como causas: alterações da mecânica pulmonar, redução da capacidade de difusão pulmonar (34, 42, 44), aumento da produção de CO_2 (33, 49), aumento do espaço morto e hiper-reatividade dos metaborreflexos (50, 51), barorreceptores e quimioreceptores (52-56).

A baixa eficiência ventilatória, caracterizada no TCPE por valores elevados do equivalente ventilatório de CO_2, ou seja, uma ventilação excessivamente alta em relação à produção de CO_2 representa um fator prognóstico negativo independente em pacientes com insuficiência cardíaca (57-61). Valor elevado do menor VE/VCO_2 (≥ 1,55 vezes o valor predito) aferido durante teste cardiopulmonar de exercício representa o principal fator prognóstico isolado em curto prazo (seis meses de acompanhamento) em pacientes com insuficiência cardíaca sistólica (3). No mesmo estudo, a combinação de elevado VE/VCO_2 com a presença de ventilação periódica foi, na análise multivariada realizada, o principal indicador de morbidade e mortalidade em curto prazo.

Na verdade, este não foi o primeiro estudo a comprovar a importância prognóstica do fenômeno de ventilação periódica em pacientes com insuficiência cardíaca. Em 2002, Corrá e colaboradores (5) acompanharam 323 pacientes com insuficiência cardíaca por cerca de 22 meses e concluíram que, a ventilação periódica é um fenômeno pouco prevalente (12%), mas que confere pior prognóstico a estes pacientes. Posteriormente, Leite e colaboradores (4) acompanharam 84 pacientes com indicação de transplante cardíaco por um período médio de 15 meses (máximo de 49 meses) e concluíram que a presença de ventilação periódica durante

teste cardiopulmonar de exercício é um preditor independente de mortalidade, tendo aumentado em 2,97 vezes o risco de mortalidade deste grupo.

Guazzi e colaboradores (62) acompanharam 156 pacientes com insuficiência cardíaca por um período médio de 27 meses e concluíram que a presença de ventilação periódica ao exercício é o principal preditor de mortalidade global e também de morte súbita cardíaca. A análise multivariada que gerou tal conclusão incluiu, além de variáveis clássicas do teste cardiopulmonar de exercício, dados ecocardiográficos (fração de ejeção do ventrículo esquerdo, volume sistólico final, massa ventricular esquerda). Por outro lado, no mesmo estudo, a análise do equivalente ventilatório de CO_2 foi o principal preditor de mortalidade por falência de bomba cardíaca. Assim, este estudo concluiu que o tratamento de pacientes com ventilação periódica ao exercício deveria priorizar estratégias antiarrítmicas.

Considerando a importância do entendimento da ventilação periódica para o embasamento teórico dos subprojetos que compõem esta tese, discutiremos em sessão isolada os mecanismos propostos para este fenômeno, conforme a seguir.

1.3.1 Ventilação periódica

A presença de oscilações ventilatórias em pacientes com insuficiência cardíaca foi descrita há quase dois séculos. A irregularidade periódica da ventilação, caracterizada por períodos de apnéia seguidos por momentos de taquipnéia até que a dispnéia seja alcançada, iniciando-se um novo ciclo semelhante, foi descrito por Cheyne em 1818 (63). Stokes, em 1854 (64), descreveu a ocorrência deste tipo de padrão respiratório em pacientes com insuficiência cardíaca, mas também naqueles com neuropatias. Desde então o termo “ventilação (ou respiração) de Cheyne-Stokes” vem sendo utilizado. Este padrão ventilatório pode ocorrer nos pacientes com insuficiência cardíaca não só durante o repouso (65), mas também durante o sono (66) e durante exercício (2-4). A ocorrência de padrão oscilatório da ventilação durante o exercício, semelhante à ventilação de Cheyne-Stokes é conhecida como ventilação periódica (Figura 6).

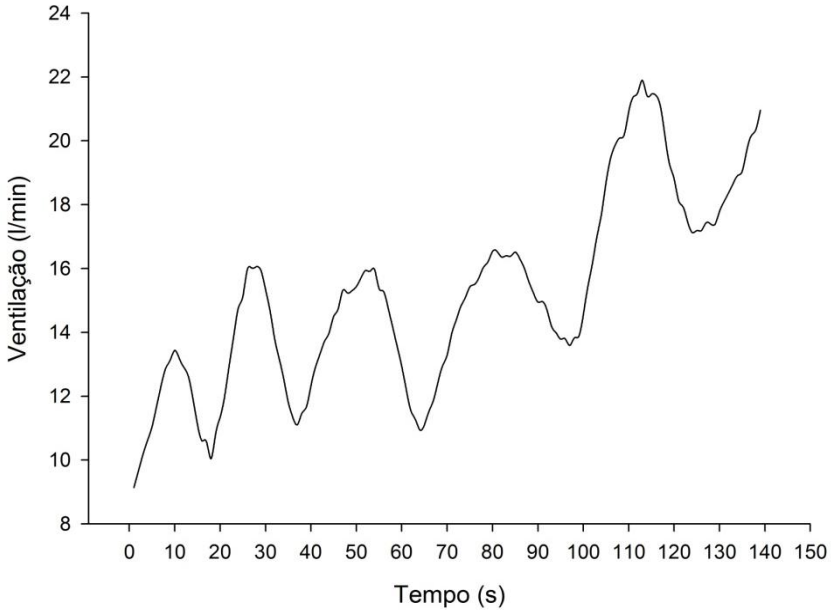

Figura 6 - Ventilação periódica
Exemplo de teste cardiopulmonar de exercício, seguindo protocolo individualizado de rampa, em que é possível identificar a ventilação periódica

1.3.1.1 Mecanismos propostos para ventilação periódica

Os mecanismos responsáveis pela ventilação periódica não estão completamente esclarecidos. Diferentes processos fisiopatológicos já foram aventados para a ocorrência deste fenônemo e podem ser agrupados em mecanismos ventilatórios (67) e metabo-hemodinâmicos (68). Segundo a hipótese ventilatória, as oscilações ventilatórias seriam conseqüentes à instabilidade dos sistemas de *feedback* que controlam a respiração (69). Esta oscilação seria secundária ao atraso entre o momento em que ocorre a alteração e sua correção propriamente dita. Entretanto, evidências mais recentes enfraquecem esta teoria. Francis e colaboradores (70) comprovaram que, apesar de a ventilação periódica causar oscilações também no VO_2 e no VCO_2, a amplitude e relação destas oscilações são complexas e variam com a intensidade do exercício. Durante exercícios de baixa intensidade as oscilações de VO_2 e VCO_2 acompanham as oscilações ventilatórias. Porém, durante o exercício em cargas mais altas os picos oscilatórios de VO_2 precedem as oscilações ventilatórias. Além disso, a reprodução voluntária de ventilação periódica por indivíduos saudáveis não foi capaz de

reproduzir as oscilações metabólicas usualmente encontradas na ocorrência espontânea deste fenômeno. A teoria metabo-hemodinâmica sustenta a hipótese de que as flutuações de VO_2 e VCO_2 em pacientes com ventilação periódica seriam secundárias às oscilações nas trocas gasosas teciduais. Considerando que o VO_2 é produto da multiplicação do fluxo sanguíneo pela diferença arteriovenosa de oxigênio, segundo esta teoria a ventilação periódica seria secundária às oscilações do débito cardíaco ou da taxa metabólica tecidual (68, 71). Alterações em quaisquer destes fatores poderiam acarretar oscilações ventilatórias através da ação de quimiorreceptores (53, 54) ou metabo-receptores (72).

Assim como na apnéia do sono, a ventilação periódica está associada com aumento da atividade simpática (73). Ponikowski e colaboradores (74) encontraram correlação inversa entre a sensibilidade periférica de quimiorreceptores e a potência de baixa freqüência da variabilidade de freqüência cardíaca, bem como a sensibilidade do barorreflexo arterial em pacientes com insuficiência cardíaca.

1.3.1.2 Critérios para identificação da ventilação periódica

Existem divergências quanto aos critérios mais adequados para definir este fenômeno (75). Mais especificamente, Corrá e colaboladores (5) definem ventilação periódica como flutuações cíclicas na V_E ocupando ao menos 60% do tempo total de exercício, com amplitude mínima 15% maior que a média das flutuações cíclicas presentes no repouso. Já Leite e colaboradores (4) descrevem o mesmo fenômeno como a presença de oscilações regulares (desvio padrão do tempo de duração de três ciclos consecutivos é, no máximo, 20% do valor da média do tempo de duração dos ciclos) com amplitude média de, no mínimo, 5l. Obviamente, o uso de diferentes critérios influencia a avaliação da incidência do fenômeno em pacientes (75). Além disso, o valor prognóstico da presença de ventilação periódica dependerá do critério utilizado (75). A inexistência de critérios definitivos para identificação da ventilação periódica, a despeito de sua relevância clínica, motivou um editorial recentemente publicado (76). Neste artigo, Fleg (76) enfatiza a necessidade iminente da universalização de critérios capazes de identificar o fenômeno da ventilação periódica e sugere que o desenvolvimento de métodos automáticos de identificação contribuiria para a disseminação do uso deste importante fator prognóstico na avaliação de pacientes com insuficiência cardíaca submetidos ao teste

cardiopulmonar de exercício. Além disso, o mesmo artigo deixa claro o potencial de uso de um método capaz não apenas de identificar, mas também de quantificar tal fenômeno. Corroborando com este pensamento desenvolvemos a linha de pesquisa que embasa todos os subprojetos que serão apresentados nesta tese. Mas antes de apresentarmos os subprojetos propriamente ditos, bem como seus resultados, descreveremos de forma sucinta alguns métodos disponíveis para o estudo da variabilidade de sinais.

1.4 **Métodos para estudo da variabilidade de sinais**

Parâmetros biológicos têm sua manutenção dentro de valores normais através do funcionamento de diferentes mecanismos de *feedback*. Assim, a maioria dos parâmetros biológicos não apresenta valores estáticos, mas sim, exibe certo grau de variação ao longo do tempo. A análise da variabilidade de sinais ganhou mais atenção na medicina a partir dos estudos que avaliaram o papel prognóstico da variabilidade da freqüência cardíaca (77, 78). Diferentes métodos estão disponíveis para a análise da variabilidade de sinais biológicos (figura 7). Nesta sessão apresentaremos alguns deles, com ênfase naqueles utilizados em alguns dos subprojetos desta tese.

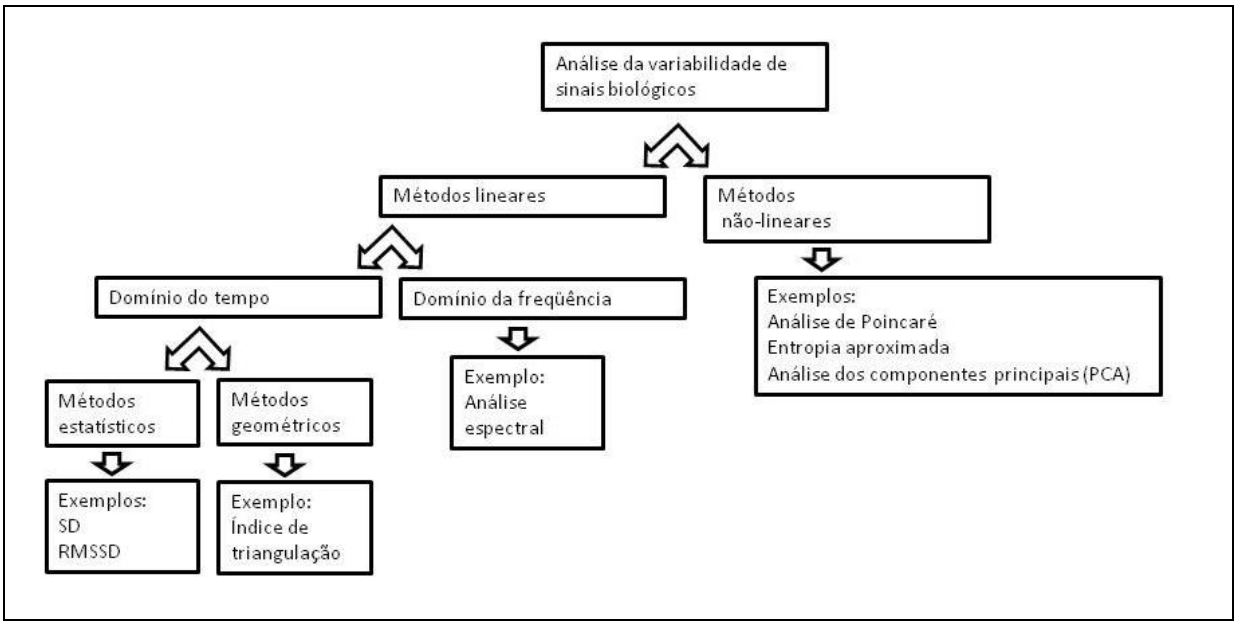

Figura 7- Principais métodos disponíveis para análise da variabilidade de sinais

1.4.1 Métodos lineares para análise da variabilidade de sinais

Os métodos lineares para análise da variabilidade de sinais podem ser classificados em métodos de análise no domínio do tempo e no domínio da freqüência. A análise no domínio do tempo avaliará a variabilidade de um sinal durante determinado período de tempo utilizando técnicas estatísticas ou geométricas (79). As técnicas estatísticas para análise no domínio do tempo avaliam a dispersão de um conjunto de dados coletados. Como exemplos de cálculos para análise da variabilidade no domínio do tempo, podemos citar: 1) desvio padrão de intervalos (SD); e 2) raiz do quadrado das médias das diferenças entre intervalos consecutivos (RMSSD). Tanto SD quando RMSSD podem ser utilizados mesmo quando o conjunto de dados a ser analisados é pequeno. Entretanto, vale enfatizar que o número de intervalos analisados, por si só, influencia a análise da variabilidade de sinais. Ou seja, a variabilidade aumenta de acordo com o número de intervalos analisados (80). Ao comparar conjuntos compostos por diferentes quantidades de dados, pode-se adotar a estratégia de normatizar a variabilidade encontrada pelo número de intervalos analisados em cada situação, ou seja, SD/n e RMSSD/n.

Métodos geométricos são bastante utilizados quando existe um grande número de intervalos anormais (interferências ou, no caso da análise da variabilidade da freqüência cardíaca, arritmias) a serem eliminados antes da realização da análise propriamente dita. Estes métodos baseiam-se na distribuição de probabilidade (histogramas) de todos os intervalos normais e quantifica a forma geométrica de tal distribuição. A facilidade para encontrar, e excluir, intervalos anormais reside no fato destes apresentarem-se como *outliers***,** ou seja, fora da forma geométrica gerada (79-81). Como este método não foi utilizado nos subprojetos desta tese, não nos aprofundaremos em sua explicação.

A análise da variabilidade no domínio da freqüência utiliza técnicas de análise espectral que computam a variância em função da freqüência (81, 82). Em geral, são identificadas quatro principais faixas de freqüência quando analisamos sinais biológicos, conforme apresentado abaixo:

- Alta freqüência: 0,15-0,40 Hz
- Baixa freqüência: 0,04-0,15 Hz

- Muito baixa freqüência: 0,003-0,04 Hz
- Ultra-baixa freqüência: <0,003 Hz

A figura 8 facilita o entendimento a respeito da decomposição espectral de um sinal de freqüência cardíaca.

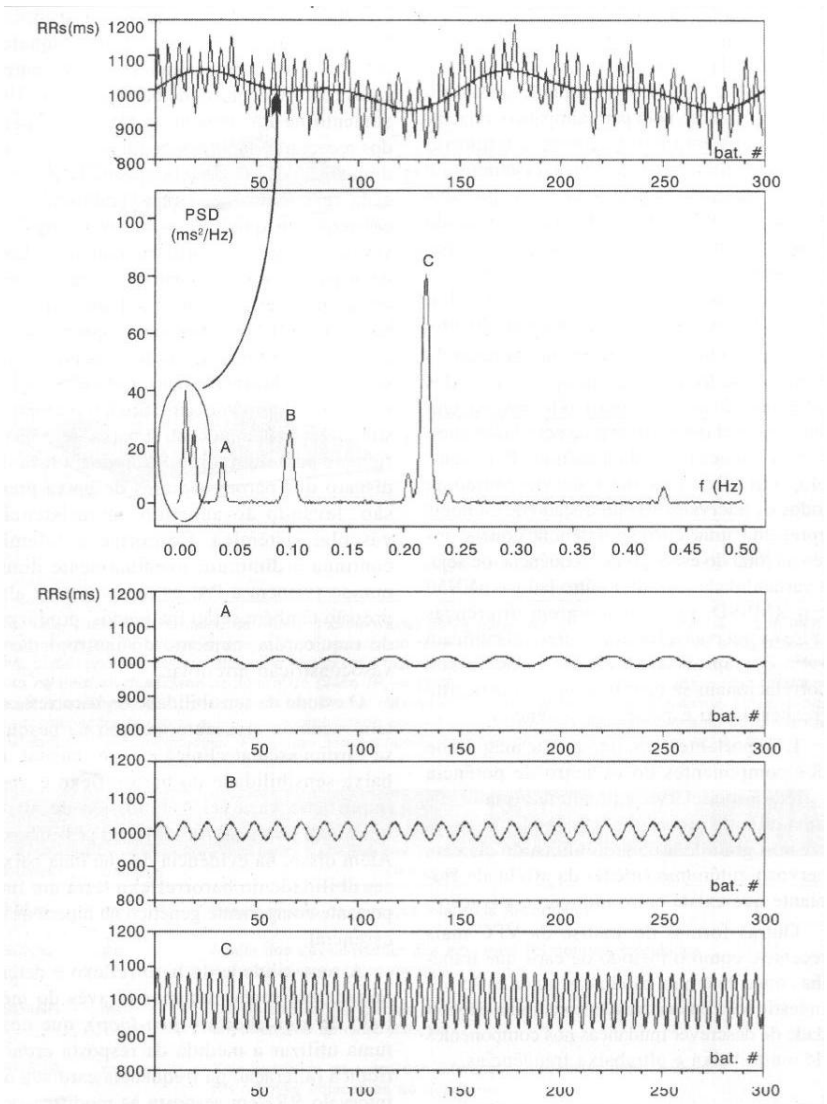

Figura 8 - Decomposição espectral de um sinal de freqüência cardíaca
O painel superior mostra o tacograma analisado contendo 300 batimentos. O segundo painel mostra o espectro de potência com quatro picos mais evidentes: o mais à esquerda (freqüência aproximada de 0,01 Hz) corresponde à linha contínua no tacograma e os picos A, B e C correspondem às harmônicas com diferentes freqüências (0,04 Hz, 0,10 Hz e 0,22 Hz, respectivamente), conforme exibido nos três painéis inferiores. Fonte: Nóbrega (81).

As figuras 9 e 10 (79) visam facilitar o entendimento da análise de variabilidade no domínio da freqüência.

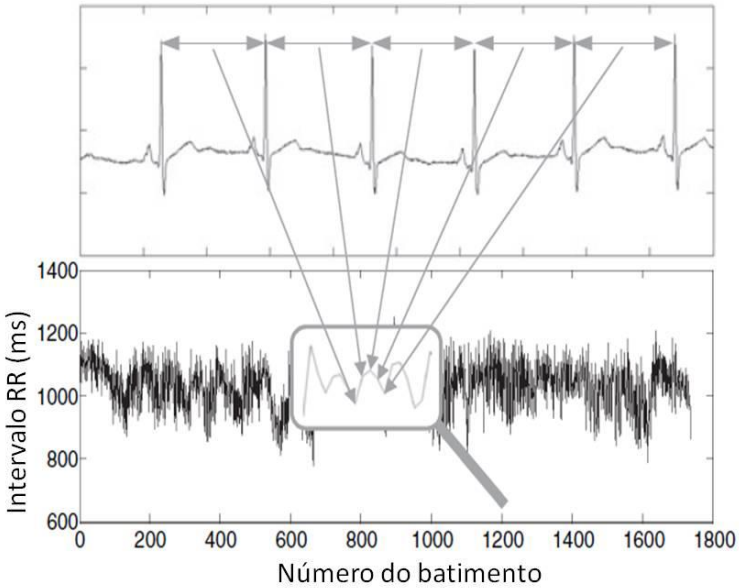

Figura 9 - Derivação do tacograma de acordo com a quantificação dos intervalos RR do eletrocardiograma
Figura adaptada de Voss e colaboladores (79)

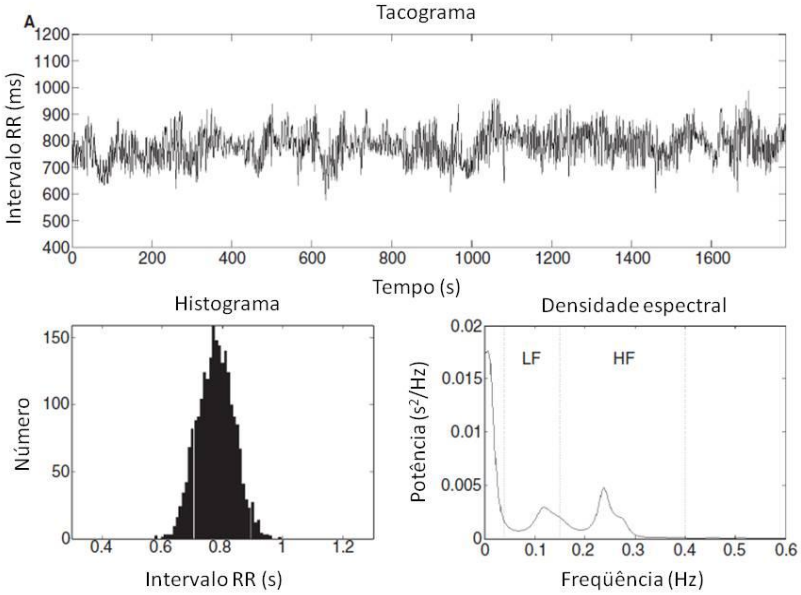

Figura 10 - Análise espectral.
A figura acima representa o tacograma de intervalos RR do eletrocardiograma de um indivíduo saudável. O histograma (abaixo à esquerda) quantifica o número de intervalos com mesma duração. Finalmente, calcula-se a densidade espectral de cada faixa de freqüência (abaixo, à direita), após a transformação da duração de intervalos em freqüências (intervalo=1/freqüência). Figura adaptada de Voss e colaboladores (79).

1.4.2 Métodos não-lineares para análise da variabilidade de sinais

Diversos métodos não-lineares estão disponíveis para a análise da variabilidade de sinais. Considerando que apenas o método da análise dos componentes principais (PCA) foi empregado em um dos subprojetos desta tese, nos deteremos a explicá-lo, não aprofundando a discussão a respeito de outros métodos não-lineares.

O PCA é uma técnica que visa diminuir a quantidade de variáveis de uma análise levando em consideração as relações estatísticas entre elas. Em um sistema de três ou mais variáveis fica difícil perceber as relações entre os dados. A representação destes sistemas fica confusa principalmente se a quantidade de coletas para cada variável for numerosa. A PCA remove dados redundantes e projeta a contribuição das variáveis para a dispersão em espaços bidimensionais. Para isso, utilizam-se técnicas estatísticas de análise multivariada de sinais, que permitem o reconhecimento de padrões específicos. O cálculo das principais componentes gera vetores (caracterizados por amplitude, sentido e direção) que carregam a informação sobre o todo (83).

2 **OBJETIVOS**

2.1 **Objetivo geral**

O objetivo geral desta tese é ampliar o conhecimento a respeito da variabilidade da ventilação-minuto durante teste cardiopulmonar de exercício em atletas, indivíduos saudáveis e pacientes com insuficiência cardíaca.

2.2 **Objetivos específicos**

- Analisar a influência de um protocolo de rampa mais rápido (20W/min) sobre as respostas cardiopulmonares de indivíduos saudáveis durante o teste cardiopulmonar de exercício realizado com membros superiores;
- Analisar a reprodutibilidade de um protocolo de rampa (20 W/min) para teste cardiopulmonar de exercício com membros superiores;
- Comparar as respostas ventilatórias, com foco na variabilidade ventilatória no domínio do tempo, de indivíduos saudáveis durante teste cardiopulmonar de exercício realizado com cicloergômetro de membros superiores e inferiores;
- Utilizar a análise de componentes principais para comparar a variabilidade de parâmetros ventilatórios em homens sedentários e atletas durante teste cardiopulmonar de exercício;
- Comparar a variabilidade ventilatória no domínio do tempo em atletas e sedentários durante teste cardiopulmonar de exercício;
- Avaliar os efeitos do exercício físico sobre a variabilidade ventilatória no domínio do tempo durante teste cardiopulmonar de exercício em indivíduos saudáveis;
- Relatar um caso de reversão da ventilação periódica em paciente com insuficiência cardíaca submetido à reabilitação cardíaca;

- Avaliar a relação entre variabilidade ventilatória e fração de ejeção em pacientes com insuficiência cardíaca.

3 ARTIGOS CIENTÍFICOS

3.1 The influence of a fast ramp rate on peak cardiopulmonary parameters during arm crank ergometry

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The influence of a fast ramp rate on peak cardiopulmonary parameters during arm crank ergometry

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Summary

The influence of a very fast ramp rate on cardiopulmonary variables at ventilatory threshold and peak exercise during a maximal arm crank exercise test has not been extensively studied. Considering that short arm crank tests could be sufficient to achieve maximal oxygen consumption (VO_2), it would be of practical interest to explore this possibility. Thus, this study aimed to analyse the influence of a fast ramp rate (20 W min^{-1}) on the cardiopulmonary responses of healthy individuals during a maximal arm crank ergometry test. Seventeen healthy individuals performed maximal cardiopulmonary exercise tests (Ultima CardiO2; Medical Graphics Corporation, St Louis, USA) in arm ergometer (Angio, LODE, Groningen, The Netherlands) following two protocols in random order: fast protocol (increment: 2 w/6 s) and slow protocol (increment: 1 w/6 s). The fast protocol was repeated 60–90 days after the 1st test to evaluate protocol reproducibility. Both protocols elicited the same peak VO_2 (fast: 23·51 ± 6·00 versus slow: 23·28 ± 7·77 ml kg^{-1} min^{-1}; $P = 0·12$) but peak power load in the fast ramp protocol was higher than the one in the slow ramp protocol (119 ± 43 versus. 102 ± 39 W, $P < 0·001$). There was no other difference in ventilatory threshold and peak exercise variables when 1st and 2nd fast protocols were compared. Fast protocol seems to be useful when healthy young individuals perform arm cardiopulmonary exercise test. The usefulness of this protocol in other populations remains to be evaluated.

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arm ergometry test; exercise test; exercise tolerance; maximal oxygen consumption

Introduction

Interest in the physiological responses to upper-body exercise has grown in recent years. Thus, arm ergometers are not as difficult to be found in exercise laboratories nowadays as they were in the last decade. Assessing upper-arm exercise, physiological responses can be very useful in different situations, ranging from patients with lower extremities disabilities (Ilias *et al.*, 2009) to high-performance athletes of kayaking, swimming and canoeing (Obert *et al.*, 1992; Forbes & Chilibeck, 2007).

Several important parameters must be defined when applying arm ergometry to evaluate athletes or patients. Some studies have focused on the influence of crank rates in attaining peak oxygen consumption during incremental arm ergometry and concluded that crank rates around 70 cycles per minute are optimal (Smith *et al.*, 2001, 2007). Other studies focused on the profile of work increment. The comparison between continuous and step protocols elicited comparable values of peak oxygen consumption, ventilation and heart rate responses (Sawka *et al.*, 1983; Washburn & Seals, 1983; Walker *et al.*, 1986; Smith *et al.*, 2004). Currently, the continuous increment ramp protocol is widely used not only in treadmill and bicycle exercise tests (Buchfuhrer *et al.*, 1983) but also in arm ergometry (Forbes & Chilibeck, 2007; Ilias *et al.*, 2009).

When small muscle groups are exercised as in arm ergometry, most individuals are not physically conditioned to sustain prolonged exercise, thus local fatigue can lead to exercise interruption before maximal oxygen consumption is achieved (Phillips *et al.*, 1998; Levine, 2008). Considering that the ramp protocol is usually programmed to achieve maximal effort around ten minutes for leg exercise (Myers & Bellin, 2000), and the suggested crank rate is 70 rpm for arm exercise, around 700 crank rotations are planned to occur during a typical maximal exercise test with the same duration of leg exercise. This protocol might be too long, potentially leading to precocious exercise interruption before peak oxygen consumption is achieved (Jameson & Ring, 2000).

Smith *et al.*, (2006) compared two different ramp rates during arm crank ergometry. They concluded that peak VO_2 and peak heart rate are not influenced by ramp rate in tests where time to fatigue is between 8 and 16 minutes. Nevertheless, they found that peak VCO_2, work rate and respiratory exchange ratio are variables that suffer influence from the ramp rate. Considering that even shorter arm crank tests could be sufficient to achieve peak VO_2, it would be of practical interest to explore this possibility. To our knowledge, the influence of a faster ramp rate in cardiopulmonary variables at ventilatory threshold and peak exercise has never been studied.

Thus, the main objective of this study was to analyse the influence of a fast ramp rate (20 W min^{-1}) on the cardiopulmonary responses of health individuals during a maximal arm crank ergometry test. As a second objective, reproducibility of the proposed fast ramp rate protocol was assessed.

Methods

Volunteers

Seventeen individuals were selected for the study among our hospital staff and students of our University. All of them were considered healthy based on clinical evaluation and a maximal exercise test in a cycle ergometer. The exclusion criteria were use of any medication, except oral contraceptives, and chronic diseases. None of the volunteers were acquainted to arm crank exercise.

All volunteers gave written informed consent to participate in the study after full explanation of the procedures and their potential risks. The investigation conformed to the principles outlined in the Declaration of Helsinki and have been approved by the Institutional Research Ethics Committee on Human Research.

Study protocol

The study included four visits of each volunteer to the Laboratory. On the first visit, volunteers underwent a maximal exercise on a cycle ergometer (Excalibur Sport, Lode, Groningen, The Netherlands), according to an individualized ramp protocol, with initial work load of 50 W and 15 s increments set to achievement of maximal effort in 8–12 min, considering individual physical activity habits, gender, body mass index and age. This first test was used for the subjects to get familiarized with the laboratory and to the cardiopulmonary exercise test facial mask (Ultima $CardiO_2$; Medical Graphics Corporation, St Louis, USA), as well as to determine each individual's exercise tolerance.

In the second and third visits, each individual performed a maximal cardiopulmonary exercise test on an electronically braked arm ergometer (Angio, Lode, Groningen, The Netherlands) following linear ramp protocols with different increments every six-seconds: fast ramp: 2 W (20 W min^{-1}); slow ramp: 1 W (10 W min^{-1}). Each individual was carefully positioned on the ergometer so that the rotational axis of the glenohumeral joint was at the same level as the axis of the ergometer's crank arm. All tests started with a warm-up period of one minute duration with a 30 W workload. Individuals were instructed to maintain a 70 rpm crank rate during both tests. The crank rate was used as the principal criterion to determine fatigue; thus, a failure to maintain a crank rate above 60 cycles per minute resulted in termination of the test.

The first three visits were separated by at least 2 days. All tests were performed in the afternoon. The potential effect of test sequence was controlled by using a counterbalanced design, where volunteers were randomly, but evenly (50%–50%) assigned to fast ramp–slow ramp or slow ramp–fast ramp protocols, in the second and third days of the study.

After the analysis of the first three tests, all individuals were invited to return to the laboratory and perform another fast ramp protocol. This test happened 2–3 months after the first trial and was performed to evaluate the reproducibility of the proposed protocol. Two of the 17 volunteers could not be contacted and did not participate in this reproducibility phase of the study. All 15 individuals kept their usual physical activity during this period.

Cardiopulmonary exercise test

Cardiopulmonary exercise tests were performed with gas exchange and ventilatory variables being analysed breath-by-breath using a calibrated computer-based exercise system (Ultima CardiO2 System). The O_2 and CO_2 analyzers were calibrated before each test using a reference gas (12% O_2; 5% CO_2; nitrogen balance). The pneumotachograph used was also calibrated, with a 3-L syringe using different flow profiles.

Oxygen consumption (VO_2), carbon dioxide production (CO_2) and minute ventilation (Ve) were registered breath-by-breath. Derived variables were calculated online (Breeze Software 6.4.1, Medical Graphics, St. Paul, MN, USA). Ventilatory threshold was identified by two experienced evaluators by the combination of the following methods: (Ilias *et al.*, 2009) at the point of upward inflection of the ventilation vs. time curve (Fig. 1a); (Forbes & Chilibeck, 2007) at the beginning of a consistent increase in the ventilatory equivalent for O_2 (minute ventilation/oxygen consumption) without a concomitant increase in the ventilatory equivalent for carbon dioxide (minute ventilation/carbon dioxide production) (Fig. 1b); and (Obert *et al.*, 1992) at the beginning of an increase in expired oxygen fraction (Fig. 1c). Ventilatory threshold was considered as the point identified by at least two of these three criteria. There was no case in which each of the criteria identified different thresholds. Peak variables were defined as the maximum individual value of each variable during the final 30 s of exercise.

During each cardiopulmonary exercise test, 12-lead electrocardiogram was continuously recorded (Cardioperfect, Welch Allin, USA) and heart rate registered.

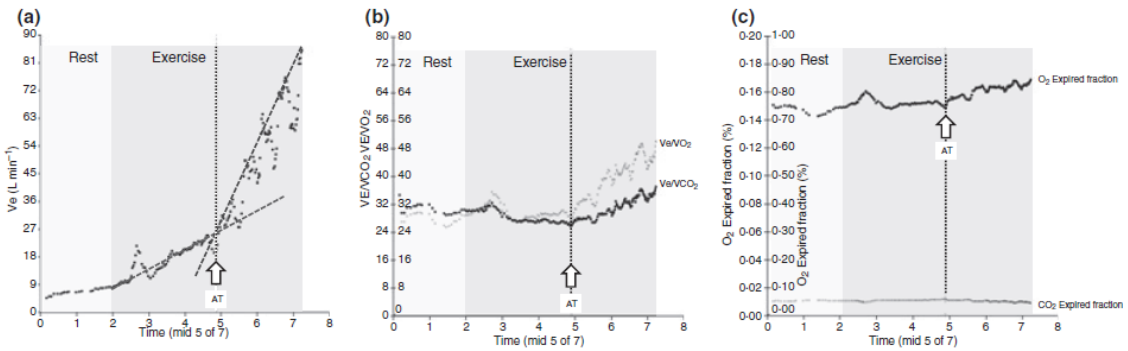

Figure 1 Example of methods used to detect ventilatory threshold. Arrows shows ventilatory threshold (AT) when each of the following methods were used: a) point of upward inflection of the ventilation vs. time curve; b) beginning of a consistent increase in the ventilatory equivalent for O_2 (Ve/VO_2) without a concomitant increase in the ventilatory equivalent for carbon dioxide (Ve/VCO_2); c) the beginning of an increase in expired oxygen fraction.

Statistical analysis

Statistical analysis was performed using the software Statistica 7.0 (Statsoft Inc, Tulsa, OK, USA). Descriptive data are presented as mean ± SD of the mean. Based on a pilot study, a sample size of 11 patients was estimated to detect a 10% difference in the exercise economy, with an alpha error of 0·05 and power of 0·90. Variables from the cardiopulmonary exercise tests showed normal distribution when analysed by the Shapiro Wilk's–W test. Variables obtained during fast and slow ramp tests were compared by the paired t-test. Reproducibility of fast ramp protocol was accessed by intraclass correlation and Bland–Altman plot. Significance was set at $P < 0·05$.

Table 1 Demographic data of volunteers included in the study (n = 17).

Male: female	8:9
Age (years)	27 ± 4
Body mass index (kg m^{-2})	23·4 ± 2·8
Peak VO_2	32·1 ± 8·4

Data presented as mean ± SE.
Peak VO_2, Peak oxygen consumption achieved in cardiopulmonary exercise test performed on a cycle ergometer.

Results

Seventeen volunteers were enrolled in the study. Their demographic data is presented in Table 1.

As expected, when fast ramp protocol was performed, maximal effort was achieved in shorter time (05′23″ ± 2′09″) when compared to the slow ramp protocol (7′59″ ± 3′53″; $P < 0.01$). Ventilatory and heart rate data in ventilatory threshold and peak exercise are presented in Table 2. Except for the peak power load, which was higher in fast ramp protocol, there were no differences between the studied protocols. As expected, peak VO2 during arm crank ergometry

Table 2 Ventilatory threshold and peak exercise data during arm ergometry following fast and slow ramp protocols.

	Fast ramp protocol	Slow ramp protocol	*P*-value
Ventilatory threshold			
VO_2 (ml kg^{-1} min^{-1})	11·78 ± 2·50	13·22 ± 5·61	0·28
VCO_2 (ml min^{-1})	799·00 ± 285·37	958·53 ± 490·58	0·12
Ve (l min^{-1})	22·88 ± 6·41	27·36 ± 12·85	0·13
Breath rate (br min^{-1})	25 ± 5	26 ± 5	0·25
Heart rate (beats min^{-1})	126 ± 12	132 ± 15	0·12
Power (W)	53 ± 20	58 ± 26	0·12
Peak exercise			
VO_2 (ml kg^{-1} min^{-1})	23·51 ± 6·00	23·28 ± 7·77	0·84
VCO_2 (ml min^{-1})	2205·12 ± .52	2076·88 ± 768·63	0·21
Ve (l min^{-1})	77·48 ± 30·87	73·52 ± 28·49	0·34
Breath rate (br min^{-1})	51 ± 12	51 ± 11	0·98
Heart rate (beats min^{-1})	166 ± 15	169 ± 20	0·82
Power (W)	119 ± 43	102 ± 39	<0·001
Respiratory quotient	1·35 ± 0·13	1·31 ± 0·21	0·26

Table 3 Ventilatory threshold and peak exercise data during arm ergometry following fast ramp protocols on two different days separated by 60 to 90 days.

	1st fast protocol	2nd fast protocol	r^2 (P)
Ventilatory threshold			
VO_2 (ml kg^{-1} min^{-1})	11·78 ± 2·50	12·71 ± 2·71	0·65 (0·009)
VCO_2 (ml min^{-1})	799·00 ± 285·37	874·33 ± 332·55[a]	0·86 (<0·001)
Ve (l min^{-1})	22·88 ± 6·41	24·98 ± 8·08	0·83 (<0·001)
Breath rate (br min^{-1})	25 ± 5	26 ± 6	0·59 (0·020)
Heart rate (beats min^{-1})	126 ± 12	129 ± 18	0·12 (>0·05)
Power (W)	53 ± 20	58 ± 23[a]	0·84 (<0·001)
Peak exercise			
VO_2 (ml kg^{-1} min^{-1})	23·51 ± 6·00	23·73 ± 6·21	0·67 (0·008)
VCO_2 (ml min^{-1})	2205·12 ± 744·52	2125·07 ± 871·12	0·91 (<0·001)
Ve (l min^{-1})	77·48 ± 30·87	72·82 ± 29·07	0·91(<0·001)
Breath rate (br min^{-1})	51 ± 12	51 ± 13	0·64 (0·013)
Heart rate (beats min^{-1})	166 ± 15	167 ± 19	0·61 (0·018)
Power (W)	119 ± 43	112 ± 41	0·98 (<0·001)

[a]t-test: $P < 0.05$ versus 1st protocol.

was smaller than in the bicycle tests (peak VO2 in arm ergometry/peak VO2 in bicycle: 75 ± 3%).

Fifteen volunteers repeated the fast protocol for reproducibility evaluation. Although VCO_2 and power during the ventilatory threshold were higher in the 2nd test, there were no differences between variables measured at peak effort when both fast ramp rate tests were compared (Table 3). Table 3 also shows the good reproducibility of most variables when the two tests that followed fast protocol were compared. Figure 2 shows Bland–Altman plots of peak variables so that test–retest reliability of fast ramp protocol can be accessed.

Discussion

The continuous increment ramp protocol is widely used in clinical and experimental settings, with a variety of ergometers being used. The American Thoracic Society/American College of Chest Physicians cardiopulmonary exercise guidelines (Ross, 2003) recommend 8–12 min as the desired duration of ramp exercise protocol. This recommendation is based on data generated from exercise tests performed in treadmill and bicycle (Buchfuhrer *et al.*, 1983). However, exercise involving smaller muscle mass, such as during arm ergometry, may lead to precocious fatigue before peak VO_2 is reached. In addition, considering practical issues, it would be desirable to employ shorter tests as long as it would be sufficient to provoke enough physiological strain so that the subject would achieve maximal VO_2. Actually, Burnley *et al.*, (2006) showed that a 3-min all-out exercise test performed on a cycle ergometer is sufficient to achieve peak VO_2. Nevertheless, all-out tests are not progressive and, thus, important information regarding ventilatory threshold cannot be obtained, diminishing their utility in clinical

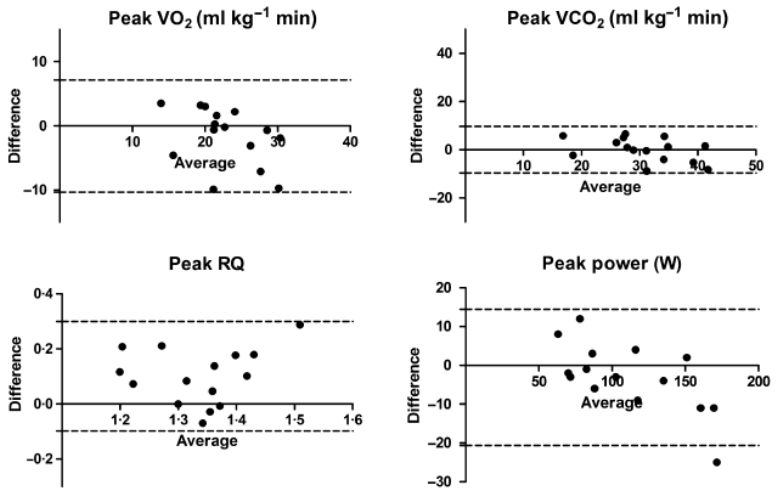

Figure 2 Bland–Altman plot of test–retest differences against test–retest means and 95% confidence interval limits for peak variables during arm ergometry following fast ramp protocol in healthy individuals. VO_2: oxygen consumption; VCO_2: Carbonic gas production; RQ: respiratory quotient (VCO_2/VO_2).

setting. Although other authors have studied fast arm ergometry protocols (Smith *et al.*, 2006), to our knowledge, the present study proposes and validates an incremental protocol where duration has not been previously tested.

In the present study, the same peak VO_2 was achieved in two different ramp rates during arm ergometry where exercise time was not the same. Fast protocol elicited the achievement of peak VO_2 with an average of 5′23″ test duration. This is shorter than the 8–12 min duration that is usually recommended for exercise incremental test in healthy subjects (?????, 2003). Except for peak power, there was no difference between peak exercise variables in both protocols, and all variables showed a high degree of reproducibility when fast protocol was repeated. Thus, this study expands the previous findings regarding ramp rates during arm ergometry tests. Smith *et al.*, (2006) found that differences in ramp rate within the range of 6–12 W/min influence the peak values of work rate, VCO_2 and respiratory quotient (RQ) but do not influence peak values of VO_2 or heart rate during arm crank ergometry. The present study has shown that ramp rate within the range of 10–20 W min^{-1} do not influence VO_2, VCO_2, RQ, ventilation, breath rate and heart rate during ventilatory threshold and peak exercise.

As previously shown in bicycle tests (Benzo *et al.*, 2007), we found that different ramp increments in arm ergometry can produce differences in peak power, although not differing in peak VO_2 values. This is important information because maximal workload is sometimes used as predictor of mortality, as in patients with chronic pulmonary obstructive disease (Martinez *et al.*, 2006). The present results reinforce the concept that the same protocol should be followed when longitudinal comparisons are performed. If the same protocol cannot be used, peak VO_2 seems to be a more reliable exercise tolerance parameter than peak power load.

A recent study evaluated the reproducibility of peak VO_2 in healthy females during incremental arm ergometry test (Leicht *et al.*, 2009) and found that, although respiratory variables exhibited substantial intra-individual variability, peak VO_2 showed high reproducibility in tests separated by 7- to 11-dayinterval. This study (Leicht *et al.*, 2009) only tested female active volunteers, who were used to arm ergometry testing. The present study has shown good reproducibility of peak and ventilatory threshold variables even in individuals who had never exercised on arm ergometer previously and with a 60- to 90-day interval between tests.

The current results are limited to healthy individuals not engaged in sports activity whose movements are predominantly performed with the arms. Considering that arm ergometry is used in individuals with lower-leg disabilities and athletes who practise upper-body sports, it is desirable that the fast protocol is tested in other specific populations.

Conclusions

Exercise exhaustion was achieved in five minutes when fast protocol was used. This protocol elicited the achievement of the same peak oxygen consumption with higher peak power when compared to the slow protocol. Fast protocol has shown high reproducibility of cardiopulmonary variables when repeated 60–90 days. Thus, fast protocol seems to be useful when cardiopulmonary exercise test in arm ergometer is performed by healthy young individuals. The usefulness of this protocol in other populations remains to be evaluated.

Conflict of interest

The authors declare no conflict of interest regarding this study.

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3.2 **Different ventilatory responses to progressive maximal exercise test performed with either arms or legs**

Ventilatory responses to arm and leg exercise

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Abstract

This study aimed at comparing respiratory responses, focusing on time-domain variability of ventilatory components during progressive cardiopulmonary exercise tests performed on cycle or arm ergometers. Twelve healthy volunteers underwent maximal cardiopulmonary exercise tests either on a cycle ergometer or on an arm ergometer following ramp protocol. Time-domain variabilities of minute ventilation (Ve), tidal volume (Vt) and respiratory rate (RR) were calculated and normalized by the number of breaths (SD/n and RMSSD/n). There was no difference in timing of breathing throughout exercise when both ergometers were compared. However, arm exercise time-domain variabilities of V_E [SD/n ($x10^3$): 124.6±2.6 vs. 93.7±2.0 l/breath, p=0.02; RMSSD/n ($x10^3$): 112.9±2.8 vs. 59.5±1.4 l/breath, p<0.001], Vt [SD/n ($x10^3$): 2.6±0.2 vs. 1.5±0.2 l/min/breath, p<0.001; RMSSD/n($x10^3$): 3.4±0.3 vs. 1.8±0.2 l/min/breath,p<0.001] and RR [SD/n ($x10^3$): 72.2±10.7 vs. 42.8±3.5 $breath^2$/min, p=0.021; RMSSD/n ($x10^3$): 90.9±14.3 vs. 38.3±3.5 $breath^2$/min,p=0.001) were greater when compared to leg exercise. The mechanisms which influence ventilatory variability during exercise remain to be studied.

Key words

Ventilatory variability, arm exercise, cardiopulmonary exercise test, leg exercise, breathing, tidal volume

Introduction

Maintenance of homeostasis is a continuous process dependent on multiple feedback mechanisms, which operate around set points. Therefore, variability of biophysical parameters is an integral aspect on physiological control. For example, cardiac output fluctuations and peripheral vascular resistance interact continuously leading to relative stability in blood pressure. Fluctuations in cardiac output can be accessed via heart rate variability, which has been extensively studied and is related to prognosis in cardiac diseases [1,2]. Not only hemodynamic, but also respiratory components fluctuate throughout time. In this context, variability of respiratory components could represent a relevant physiological phenomenon, although rarely addressed [3,4].

In the last decade, heart-lung interactions have been identified as a key issue in heart failure [5]. Several studies have suggested that ventilatory parameters analysis during exercise can add relevant information regarding the prognosis of heart failure patients [6-9]. Despite the increasing number of recent publications discussing ventilatory abnormalities in heart disease, little is known about the physiologic timing of breathing during exercise in healthy people. A recent study [10] normalized timing of breathing in healthy people of different ages and gender during exercise. They found that although respiratory cycles get short from rest to peak exercise, the relationship between inspiratory and expiratory times is kept constant during incremental cycle ergometry [10].

Gas exchange analysis during exercise can confer relevant information when patients are evaluated. In this setting, not only classic respiratory parameters, such as ventilatory equivalents, but also the occurrence of periodic breathing can confer relevant clinical and prognostic information in heart disease [4,9]. Periodic breathing is an abnormal pattern of ventilation, characterized by cyclic hyperpnea and hypopnea during exercise [11]. Authors use slight different criteria for the diagnosis of periodic breathing [12]. Moreover, clinical experience shows that some heart failure patients exhibit ventilatory oscillations during exercise test that, although does not seem to be really normal, does not comply to any of the previously established criteria for periodic breathing [4,13]. The absence of an universally accepted definition of periodic breathing, the need to manually identify this phenomenon and the inexistence of a method that enables quantitative assessment of ventilatory

oscillations during exercise prevents the widespread use of periodic breathing as a prognostic criteria in heart failure [14]. In this setting, time domain variability appears as an useful mathematical tool that could be applied to quantify ventilatory variability during exercise.

During upper-body dynamic exercise, thoracic and arm movements may influence breathing. Therefore, not only clinical status but also the type of exercise performed could influence timing of breathing and the variability of ventilation during exercise. Assessing the physiological responses to upper-body exercise can be very useful in different situations, ranging from patients with lower extremities disabilities [15] to high-performance kayaking, swimming and canoeing athletes [16,17].

For that reason, the present study was designed to compare respiratory responses, focusing time-domain variability of ventilatory variables (respiratory rate, minute-ventilation and tidal volume) of healthy individuals during progressive cardiopulmonary exercise tests performed in cycle and arm ergometer.

Material & Methods

Volunteers

Twelve individuals were selected for the study among our hospital staff and students of our University. All of them were considered healthy based on clinical evaluation and having undergone a maximal exercise test in a cycle ergometer. The exclusion criteria were the usage of any medication, except oral contraceptives; chronic diseases. None of the volunteers were acquainted to arm crank exercise. Although individuals have previous experience with leg ergometers, none of them used to perform leg exercise regularly.

All volunteers gave written informed consent to take part in the study after full explanation of the procedures and their potential risks. The investigation conformed to the principles outlined in the Declaration of Helsinki and have been approved by the Institutional Research Ethics Committee on Human Research.

Study protocol

The study included three afternoon visits of each volunteer to our laboratory. As the volunteers were more used to perform exercise in cycle than arm ergometer, on the first visit, each volunteer performed a maximal exercise test on an arm ergometer. This first test was performed so that subjects could get familiarized to the laboratory equipment, arm ergometer and to the facial mask used for cardiopulmonary exercise test

On the second visit, volunteers underwent a maximal exercise test on a cycle ergometer (Excalibur Sport, LODE, Netherlands), according to an individualized ramp protocol, with initial work load of 50 W and linear increments set to achieve maximal effort in 8 to 12 minutes, considering individual physical activity habits, gender, body mass index and age. Individuals were instructed to maintain the pedaling frequency of 60±5 RPM.

During the third visit, each individual performed a maximal cardiopulmonary exercise test on electronically-braked arm ergometer (Angio, LODE, Netherlands) following linear increment ramp protocol (20W/min), as previously validated [18]. All tests started with a one minute warm-up period with a workload of 30 W. Each individual was carefully positioned at the ergometer so that the rotational axis of the glenohumeral joint was at the same level as the ergometer's crank arm axis. Individuals were instructed to keep a 60±5 RPM crank rate. Crank rate was used as the principal criterion to determine fatigue, thus, a failure to maintain a crank rate above 50 RPM resulted in termination of the test.

Cardiopulmonary exercise test

Cardiopulmonary exercise tests were performed with gas exchange and ventilatory variables being analyzed breath-by-breath using a calibrated computer-based exercise system (Ultima CardiO2 System, Medical Graphics Corporation, USA). The O_2 and CO_2 analyzers were calibrated before each test using a reference gas (12% O_2; 5% CO_2; nitrogen balance). The pneumotachograph used was also calibrated, with a 3L syringe using different flow profiles.

During each cardiopulmonary exercise test, a 12-lead electrocardiogram was continuously recorded (Cardioperfect, Welch Allin, USA) and the heart rate registered.

Oxygen uptake (VO_2); carbon dioxide output (CO_2), tidal volume (Vt), inspiratory time (Ti), expiratory time (Te) and total respiratory time (Ttot) were breath-by-breath registered. Derived variables [respiratory rate (RR), minute ventilation (Ve), respiratory equivalents for oxygen (Ve/VO_2) and carbon dioxide (Ve/VCO_2)] were calculated online (Breeze Software 6.4.1, Medical Graphics, USA). RR, Ve, Ttot, Ti, Te, Ti/Ttot were analyzed at 40%, 60%, 80% and 100% of maximal ventilatory intensity for each exercise test.

Time domain variability of Ve, RR and Vt during exercise was calculated as the standard deviation (SD) and the root mean square of successive differences

(RMSSD) of each variable. Considering that the test's duration could have influenced these results, both calculations were normalized by the number of breaths (SD/n and RMSSD/n, respectively) [19].

Statistical Analysis

Statistical analysis was performed using the software Statistica 7.0 (Statsoft Inc, USA). Descriptive data are presented as mean ± standard error of the mean. Variables from the cardiopulmonary exercise tests showed normal distribution when analyzed by the Shapiro Wilk's W test. Variables obtained during leg or arm exercise at different moments (40%, 60%, 80% and 100% of maximal ventilation) were compared by Anova two-way followed by post-hoc Bonferroni test. Time-domain ventilatory variability variables during exercise tests with both ergometers were compared by paired bicaudal Student T test. Significance was set at $p<0.05$.

Results

Twelve healthy individuals completed the study (6 male; age: 27±1 years; body mass index: 22,7 ± 0,7 kg/m^2). All tests were maximal, with respiratory quotient greater than 1.1 (table 1). Peak exercise variables in both tests are shown in table 1. The same peak heart and respiratory rates were achieved in both types of exercise, but with higher peak VO_2, minute ventilation, tidal volume and power load during graded maximal leg exercise, as expected. The analysis of ventilatory variables normalized to peak power (table 1), clearly shows that the same power load elicits greater ventilatory responses to arm exercise when compared to leg exercise.

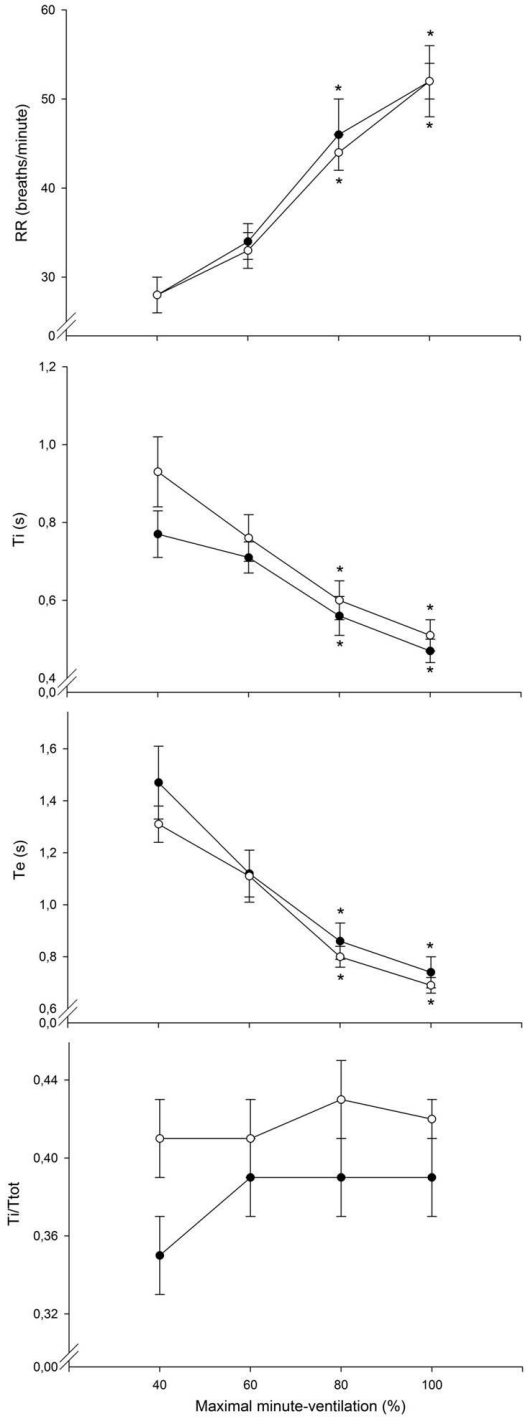
Table 1. Peak exercise data during graded maximal cardiopulmonary leg or arm exercise test (n=12)

	Arm exercise	**Leg exercise**	***P* value**
VO_2 (mL/kg min)	26.0 ± 1.8	37.8 ± 1.8	<0,001
VCO_2 (mL/kg min)	34.0 ± 2.5	46.2 ± 2.2	<0.001
Ve (L/min)	78.9 ± 9.3	99.9 ± 32.1	<0.001
Respiratory rate (breaths/min)	52 ± 4	52 ± 2	0.80
Vt (L)	1.53 ± 0.18	1.95 ± 0.16	<0.01
Heart rate (beats/min)	167 ± 4	177 ± 5	0.13
Power (W)	116 ± 13	225 ± 20	<0.001
Respiratory quotient	1.37 ± 0.03	1.26 ± 0.03	0.20
Ve/Power (L min/W)	0.69 ± 0.05	0.45 ± 0.02	<0.001
Respiratory rate/ Power (breaths min/W)	0.50 ± 0.06	0.25 ± 0.02	<0.001
Vt/Power (mL/W)	13.27 ± 0.74	8.77 ± 0.32	<0.001

VO_2: Oxygen uptake; VCO_2: Carbon dioxide output; Ve: minute-ventilation; Vt: tidal volume.

P value refers to the result of paired student's T test

Figure 1. Timing of breathing during incremental exercise performed with legs (white circles) or arms (black circles) expressed as a function of relative ventilatory responses in healthy volunteers (n=12).



Legend: Vertical bars represent standard errors. * *p*<0.01 vs. 40% same ergometer
RR: respiratory rate; Ti: inspiratory time; Te: expiratory time; Ttot: total respiratory time

Figure 1 presents that there was no difference in timing of breathing during graded maximal exercise test when both ergometers were compared (p>0,05). Interestingly, table 2 shows a greater time-domain variability of ventilatory variables during arm crank exercise if compared to leg exercise.

Table 2. Time-domain ventilatory variability of healthy individuals (n=12) during graded maximal cardiopulmonary arm or leg exercise tests.

Variable (x10^3)	**Arm exercise**	**Leg exercise**	***P* value**
Respiratory rate			
SD/n (breath^2/min)	72.2 ± 10.7	42.8 ± 3.5	0.021
RMSSD/n (breath^2/min)	90.9 ± 14.3	38.3 ± 3.5	0.001
Tidal volume			
SD/n (l/min/breath)	2.6 ± 0.2	1.5 ± 0.2	<0.001
RMSSD/n (l/min/breath)	3.4 ± 0.3	1.8 ± 0.2	<0.001
Minute-ventilation			
SD/n (l/breath)	124.6 ± 2.6	93.7 ± 2.0	0.002
RMSSD/n (l/breath)	112.9 ± 2.8	59.5 ± 1.4	<0.001

SD: standard deviation; RMSSD: root mean square of successive differences; n: total number of breaths during exercise test

P value refers to the result of paired student's T test

Discussion

Timing of breathing in healthy volunteers whose ages ranged from 20 to 80 years-old have previously been described [10]. This normative study [10] provided us with clinical relevant reference values for interpretation of timing of breathing during maximal graded exercise in cycle ergometer. Nevertheless whether similar results results would be found in other types of exercise was not known. The present study shows that the type of exercise (leg or arm dynamic exercise) does not influence timing of breathing during maximal progressive exercise test, even during maximal minute-ventilation. A previous study [20] found that heavy arm exercise elicited greater respiratory rate than leg exercise. We believe that the results [20] concerning respiratory rate, inspiratory and expiratory times during heavy exercise differ from ours because the “heavy exercise” concept was different in both studies. Our study compared arm and leg exercise in the same fraction of maximal minute-ventilation, whilst in theirs, absolute minute-ventilation values were used for comparison. Considering that peak minute-ventilation is higher during leg exercise than arm exercise, same absolute minute-ventilation corresponds to different exercise intensities when arm and leg exercises are to be compared [20].

Considering that peak power output is much higher in leg than in arm exercise, it seems adequate to normalize variables to peak power output before any comparison is done. Arm exercise elicits higher minute-ventilation, respiratory rate and tidal volume when compared to leg exercise at the same power load. This is in agreement with the study by Sawka et al [21] who found higher minute-ventilation during arm exercise when compared to leg exercise at the same absolute oxygen uptake.

Cardiopulmonary exercise test is increasingly being used as a diagnostic and prognostic tool in clinical practice. Recently, more attention is being paid to the exercise ventilatory responses on patients with heart disease. A recent study [9] emphasized the role of ventilatory equivalent for carbon dioxide output (Ve/VCO_2) in determining prognosis of heart failure patients. After evaluation of different classical prognosis predictors, the same study [9] concluded that the most powerful prediction model of early mortality and morbidity in heart failure is the combination of elevated lowest Ve/VCO_2 and the presence of periodic breathing during exercise test. Nevertheless, the absence of a universally accepted definition of periodic breathing and the need to manually identify this phenomenon impairs the widespread use of

periodic breathing as a prognostic criteria in heart failure [14]. Whether a graded or quantitative assessment of periodic breathing would be able to refine the prognostic information usually given by the presence or absence of this phenomenon is unknown. Considering that periodic breathing is diagnosed by different criteria which, in summary, depict the variability of ventilation throughout a graded exercise test, we decided to apply mathematical methods traditionally used to evaluate time-domain heart rate variability in order to analyze ventilatory variability during exercise. We have previously used the same methods in cardiac disease [19] and found that breath-by-breath minute-ventilation and respiratory rate variabilities during exercise are inversely correlated to left ventricular ejection fraction in heart failure. Hence, patients with lower ejection fraction exhibit greater ventilatory variability during a graded symptom-limited exercise test. In the present study, appling the same methods, we found that ventilatory variability of healthy individuals is greater during arm exercise when compared to leg exercise. To our knowledge, this is the first study to evaluate ventilatory variability during arm exercise, which was not designed to determine the mechanisms of this phenomenon. It is important to note that all volunteers evaluated in this study were healthy. Therefore, mechanisms involved in Cheyne-Stokes respiration and periodic breathing, such as hypocapnia, increased central and peripheral chemosensitivity [22] and pulmonary blood flow fluctuations [23], which are considered key mechanisms in heart failure, would probably not be useful in understanding physiological ventilatory variability during exercise in healthy subjects. But why are the respiratory variables so unstable during exercise and why are there differences between time-domain ventilatory variability when leg and arm exercise are compared? The responses of respiratory system to physical exercise represent one of the main challenges in the study of homeostasis [24]. There seems to be a very sophisticated respiratory controller system capable of integrating multiple afferent and efferent signals in adapting the ventilatory pattern during exercise [24].

Arm exercise elicits greater lactate accumulation than leg exercise at the same power output [25], greater rate of perceived effort and greater stimulation to breathe from force sensing mechanoreceptors in the joints or from greater sympathetic stimulation [25,26]. Such factors are usually accepted as reasons for greater sensations of breathlessness during arm work [20]. The greater perturbation in autonomic system, blood pH and effort perception elicited by arm exercise when compared to leg exercise at the same output could lead to an even more difficult

equilibrium in respiratory responses. Although breathlessness sensation was not quantified, this could explain the greater respiratory variability during arm than leg exercise.

Arm exercise elicits greater inputs from muscular afferent fibers than leg exercise, leading to different autonomic responses when both types of exercise are to be compared. This difference is independent of active muscle mass but it relies on the number and/or sensitivity of afferent receptors in the upper body.

Autonomic modulation potentially influences ventilatory variability during exercise. A phenomenon called cardioventilatory coupling has been proposed and describes a condition where heartbeats entrain the respiratory rhythm, triggering inspiratory onset by unknown cardiovascular afferent pathways [27,28]. Thus, changes in autonomic cardiovascular modulation and heart rate variability could potentially influence respiratory rhythm and ventilatory variability. Few studies have compared autonomic modulation during arm and leg exercise. There is a higher level of sympathetic nervous activity during maximal [29] or submaximal [30] lower body exercise when compared to upper body exercise.

During steady-state moderate exercise, heart rate variability is reduced from resting levels, but with greater heart rate variability during upper-body exercise when compared to lower-body [31]. The greater heart rate variability during arm-exercise might reflect greater respiratory sinus arrhythmia [31]. We have studied time-domain variability of ventilation during a graded maximal exercise test, from rest to peak exercise. Hence, our analysis included moments of the exercise test when vagal activity is minimal. Nevertheless, the higher vagal modulation during arm exercise from rest to, at least, moderate effort may have influenced ventilatory variability throughout the test. Although the evaluation of autonomic modulation during exercise is beyond the scope of the present study, this is a potential mechanism and remains to be studied.

Limitations

Some operational and technical aspects could have influenced the results reached in the present study. Subjects were not submitted to rest pulmonary function tests before entering the study. Considering that none of them had any past history of pulmonary disease or smoking, and that tests by the same volunteer were used for comparison, the absence of rest pulmonary function tests does not seem to be a major issue influencing the present results. All breath-by-breath data was collected

by a face mask. Thus, the use of face mask could not explain the different results when arm and leg exercise were compared. The use of a mouthpiece and nose clip is known to influence the depth and rate of breathing [32]. Although this effect appears to be restricted to lower levels of exercise [33], it seems reasonable not to interchangeably compare ventilatory variability results recorded using mask, mouthpiece or canopy.

Trained volunteers sometimes tend to match their breathing pattern to the cycling rate [34]. Pedaling and arm crank rotations rates were fixed in values greater than 60 cycles per minute. Considering that respiratory rates have not reached such high frequencies, it seems that cycling rate could not have influenced ventilatory variability in the present study.

Conclusions

Timing of breathing is not influenced by the type of exercise performed when arm and leg dynamic exercises were compared. Time-domain ventilatory variability of young, healthy individuals was greater during maximal graded exercise test performed in arm ergometer when compared to leg ergometer. The mechanisms that influence ventilatory variability during exercise remain to be studied.

Perspective

Time-domain analysis may be used as a simple tool to quantify variability of minute-ventilation, tidal volume and respiratory rate during exercise. This technique is potentially useful to evaluate heart and lung interactions during exercise.

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3.3 **Principal components analysis to evaluate ventilatory variability: comparison of athletes and sedentary men**

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ORIGINAL ARTICLE

Principal components analysis to evaluate ventilatory variability: comparison of athletes and sedentary men

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Abstract The present work quantifies, through principal components analysis (PCA) the relationships among the variability of breath-by-breath ventilatory parameters [minute-ventilation (VE), tidal volume (Vt), and respiratory rate (FR)] during a maximal progressive exercise test. The results show that the first and second eigenvalues of the covariant matrix contains almost 90% of the variables' variance possible to see through the PCA, which means that the problem can be reduced by a two-dimensional analysis. The results show a close similarity between the global variability in two groups test, athletes and sedentary (control). For the athletes group, the parameter Vt is responsible for the high VE variability values while in the sedentary group the FR is more relevant for VE variability. The result improves the knowledge about respiratory variability during exercise, showing that Vt's and FR's variabilities contribute in different ways to global ventilation variability during a maximal cardiopulmonary exercise test in athletes and sedentary men.

Keywords PCA · Variability · Ventilation · Comparison

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1 Introduction

Homeostasis maintenance is a continuous process that depends on multiple feedback mechanisms which operate around set points. Thus, biophysical parameters variability is an integral aspect of physiological control and their analyses are useful so as to detect abnormal patterns which may indicate the worst prognosis in some diseases. For instance, low heart rate variability indicates bad prognosis in heart disease [10, 11]. Respiratory parameters could represent a relevant physiological phenomenon for this subject theme, although rarely addressed. The ventilation's oscillation in steady-state conditions is usually caused by instability of respiratory chemical control loops [1]. The concept that some diseases are diagnosed or prognosticated [5, 13, 18, 19] by the incidence of minute-ventilation (VE) oscillations in different situation yields the physiological description patterns and the conception of methods capable of detecting abnormalities in ventilatory fluctuations.

More specifically, the occurrence of VE oscillations during exercise, named periodic breathing, exhibits important prognostic information in patients with heart failure [12, 19]. Clinical practice shows that some patients may exhibit oscillations in VE exercise without complying with the strict criteria of periodic breathing [2, 11]

The absence of a universally accepted definition of periodic breathing and the need to manually identify this phenomenon are technical challenges to the widespread use of periodic breathing as prognostic criteria in heart failure [7]. Whether a graded quantitative assessment of periodic breathing would provide more detailed prognostic information than the presence or absence of ventilatory oscillations during exercise is a question that remains to be answered [7]. We have recently found that there is an inverse relationship between the time-domain VE variability during exercise and

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the ejection fraction in heart failure patients without periodic breathing [2]. The ventilatory variability evaluation may add information in the assessment of breathing oscillations throughout the exercise. It is imperative to understand the physiologic pattern of any new prognostic variable so that pathological variations can be identified.

There are different available methods that permit biological signals analysis. Some of them can be useful to determine patterns in the general behavior of the measures and, from wavelets to statistical procedures, some of them can provide information on how the body works in terms of external or internal parameters [6, 14, 16, 17]. Indeed, in ventilation variability some methods are proposed but without a unique choice, usually due to the high analysis complexity which involves a strong correlation between different parameters collected in the experimental procedure [8, 15, 20]. This fact leads us to propose principal components analysis (PCA) to determine the correlation between different parameters obtained in a ventilation data collection.

Exercise training confers adaptations that are capable of altering the responses to a single exercise section. The adaptation of respiratory variability to physical training is still unknown. Considering the eminent importance of respiratory variability analysis and the unavailability of a method to perform such analysis, the present article aims at comparing the variability of ventilatory parameters [VE, respiratory rate (FR), and tidal volume (Vt)] on sedentary healthy men and athletes during a progressive maximal exercise test, using the PCA.

2 Methods

2.1 Volunteers

Eighteen male volunteers (9 sedentary and 9 athletes) were invited to participate in the study. All of them were considered healthy after medical evaluation which consisted of anamnesis and physical examination. None of them were smokers or had been in regular use of any kind of medication. Sedentary men were not involved in any regular physical activity. Athletes were professional soccer players from the same soccer team in Rio de Janeiro, Brazil.

2.2 Study protocol

All volunteers provided written informed consent to participate in the study after full explanation of the procedures and their potential risks. The investigation conformed to the principles outlined in the Declaration of Helsinki and have been approved by the Institutional Research Ethics Committee on Human Research.

The groups performed a maximal cardiopulmonary exercise test in a treadmill (Trackmaster 30 × 30, USA) following an individualized ramp protocol. Exercise test was interrupted whenever the perceived exertion reached grade 10 in a modified BORG scale. Cardiopulmonary exercise tests were performed with gas exchange and ventilatory variables being analyzed breath-by-breath using a calibrated computer-based exercise system (Ultima CardiO2 System, Medical Graphics Corporation, USA). The O_2 and CO_2 analyzers were calibrated before each test using a reference gas (12% O_2; 5% CO_2; nitrogen balance). The pneumotachograph used was also calibrated, with a 3 l syringe using different flow profiles. During each cardiopulmonary exercise test, a 12-lead electrocardiogram was continuously recorded (Cardioperfect, Welch Allin, USA) and heart rate registered. Oxygen consumption (VO_2); carbon dioxide production (CO_2), Vt, and respiratory rate or frequency (FR), were registered breath-by-breath. VE was calculated online (Breeze Software 6.4.1, Medical Graphics, USA). Specifically, we can understand the measures as follows: VE: volume of air exhaled from the lungs in 1 min, respiratory frequency (FR): the number of breaths in 1 min, and Vt: volume of air exhaled from the lungs in one breath. Thus, the sum of Vts from all breaths in a minute is equal to VE. In the case where Vt does not vary, VE is the product of respiratory frequency and Vt.

Principal components analysis

The principal components method used in this analysis consists in separate the ensemble in two distinct groups: athletes and control. This method was chosen based on its capacity to analyze the relationship between parameters that move together. This occurs in consequence of the instrumentation system which collects ventilator parameters. As main result, there is a redundancy of information which can be simplified in a single variable. Principal components method is a rigorous method for achieving this simplification. The method generates new variables called principal components. Each principal component is related to the original value trough a linear combination of each

Table 1 Example of data used in PCA method

Athlete/control (data)	VE	Vt	FR
1	117.2	1.94	50.85
	⋮	⋮	⋮
	47.7	2.3	32.09
⋮	129.4	1.88	50.85
	⋮	⋮	⋮
	47.4	2.9	36.36
N	128.4	2.94	41.1
	⋮	⋮	⋮
	35.7	1.54	40

experimental value. The analysis is focused on the relation of the first and second component, where the first principal component is a projection of each observation in a single axis in space with the maximum variance among all possible choices, whereas the second principal component is another axis in space, perpendicular to the first (Table 1).

The data contains the pieces of information as showed in Table 1. Where the columns are the ventilation parameters VE, Vt, and FR and the rows the values obtained from the equipment. Starting with this data for each group, the standard deviation was calculated for each parameter, this value was used in order to normalize the data. The covariance matrix and the linear combination of the variables were used to calculate the coefficients of the PCA method, for this the data was standardizing subtracting the mean of each parameter from the same row of data and divide by each standard deviation. The covariance between two variables is given by:

$$\mathrm{cov}(X,Y) = \frac{\sum_{i=1}^{n}\left(X_i - \overline{X}\right)\left(Y_i - \overline{Y}\right)}{n-1}, \tag{1}$$

which result in a covariance matrix given by Eq. 2.

$$C = \begin{pmatrix} \mathrm{cov}(X,X) & \mathrm{cov}(X,Y) & \mathrm{cov}(X,Z) \\ \mathrm{cov}(Y,X) & \mathrm{cov}(Y,Y) & \mathrm{cov}(Y,Z) \\ \mathrm{cov}(Z,X) & \mathrm{cov}(Z,Y) & \mathrm{cov}(Z,Z) \end{pmatrix} \tag{2}$$

The eigenvectors of the C are showed in the matrix of coefficients (M_{coef}), separated in two groups. The matrix of coefficients for athletes and control group are showed in Eqs. 3 and 4.

$$M_{\mathrm{coef(athletes)}} = \begin{pmatrix} 0.6818 & -0.043888 & -0.73022 \\ 0.4554 & 0.80666 & 0.37672 \\ 0.5725 & -0.58939 & 0.56997 \end{pmatrix} \tag{3}$$

$$M_{\mathrm{coef(control)}} = \begin{pmatrix} 0.6826 & -0.015905 & -0.73062 \\ 0.53864 & -0.66471 & 0.51771 \\ 0.49389 & 0.74693 & 0.44517 \end{pmatrix} \tag{4}$$

The scores were calculated from this matrix and the distribution of the first and second component along the

Table 2 Demographic and anthropometric data of volunteers ($n = 18$)

Variable	Control ($n = 9$)	Athlete ($n = 9$)	P value*
Age (years)	26 ± 6	22 ± 2	0.128
Weight (kg)	77.7 ± 11.0	70.6 ± 1.3	0.134
Height (m)	1.75 ± 0.06	1.75 ± 0.03	0.866
BMI (kg/m^2)	25.4 ± 3.04	23.05 ± 1.14	0.064
Peak VO_2 (ml/kg/min)	42.64 ± 5.62	47.81 ± 0.56	0.028

* Comparison between groups by student's t test

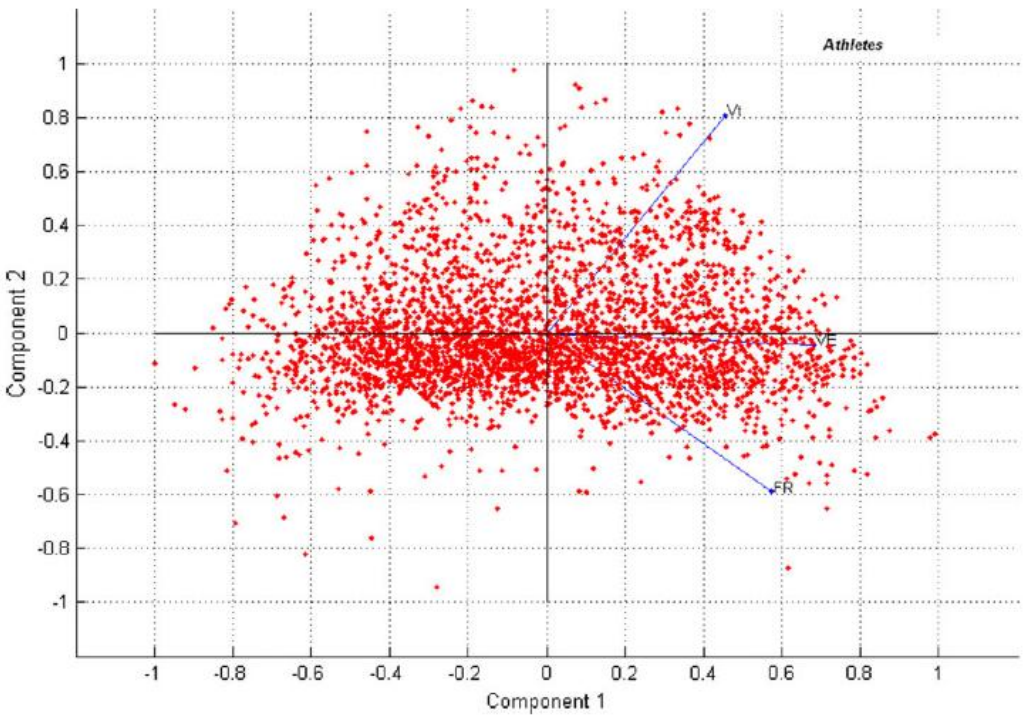

Fig. 1 Principal components analysis for the VE, Vt, and FR parameters in athletes group, where x-axis is the first component and y-axis is the second component for all values of time

axis generated the variability relation inner group. More specifically, the scores of each variable can be projected in a reduced coordinate system, in our case in two dimensional without loss of information, which contain the global behavior about the overall variance of the measures.

2.3 Statistical analysis

Statistical analysis was performed using the software Statistica 7.0 (Statsoft Inc, USA) for the demographic and anthropometric parameters. Descriptive data are presented as mean ± SD of the mean. Variables from the cardiopulmonary exercise tests showed normal distribution when analyzed by the Shapiro–Wilk's W test. Exercise variables in both groups were compared by paired bicaudal Student's t test. Significance was set at $P < 0.05$.

3 Results

All tests were considered maximal and reached a respiratory quotient greater than 1.10 (athletes: 1.34 ± 0.01; sedentary: 1.29 ± 0.13; $P = 0.38$). The demographic and anthropometric characteristics of both groups are described in Table 2.

Figure 1 shows the VE, FR, and Vt values during the progressive maximal exercise test in athletes. It can be observed that FR and Vt contribute significantly more in time analysis. More specifically, the variances of first and second components for this group are 2.1365 and 0.85376, respectively. The third component assumes the value 0.0097691. It is important to notice that the first component has, approximately, 71.2% of the total data variance and the second component has 28.4%. Together, the first and second components are responsible for 99.6% of the variance.

These results show a lower data dispersion when this group (Fig. 1) is compared with the control group in Fig. 2. In sedentary men the Vt parameter has a small contribution for the group, which can be observed by the length of the vector Vt, the higher contribution for the variance came from the FR. The vectors are a projection of three independent components in a two-dimensional space. The coordinates of each vector in Fig. 1 are VE = (0.6818, −0.0438); Vt = (0.4554, 0.89066); and FR = (0.5725, −0.5893) where the first value corresponds to the x-axis and the second value to the y-axis.

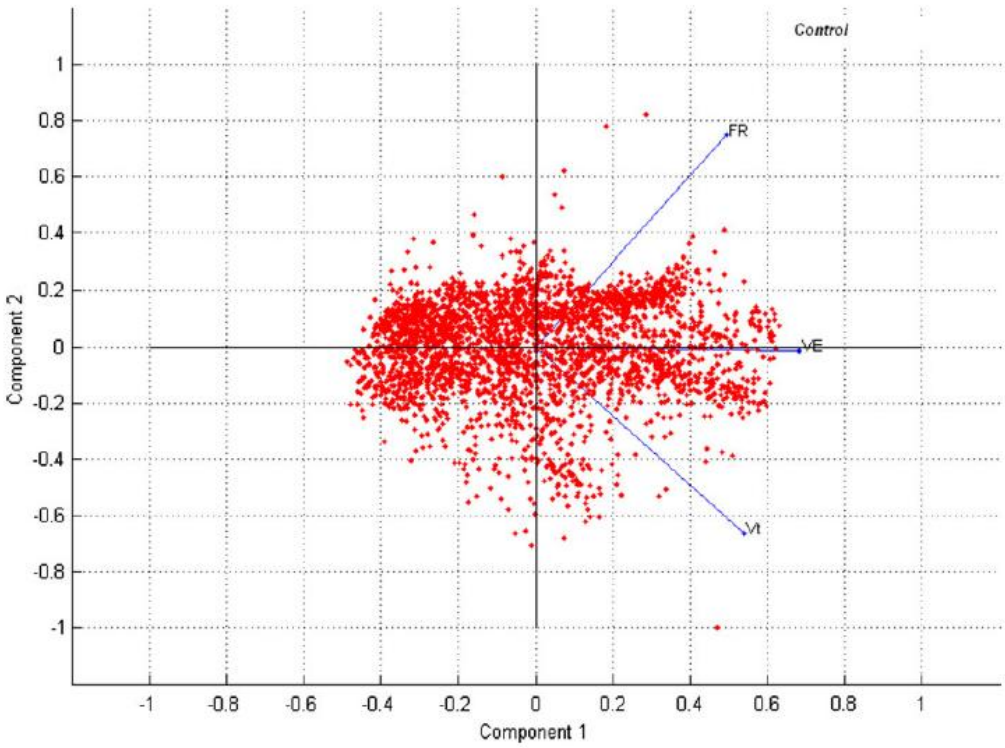

Fig. 2 Principal components analysis for the Ve, Vt, and FR parameters in control group, where x-axis is the first component and y-axis is the second component for all values of time

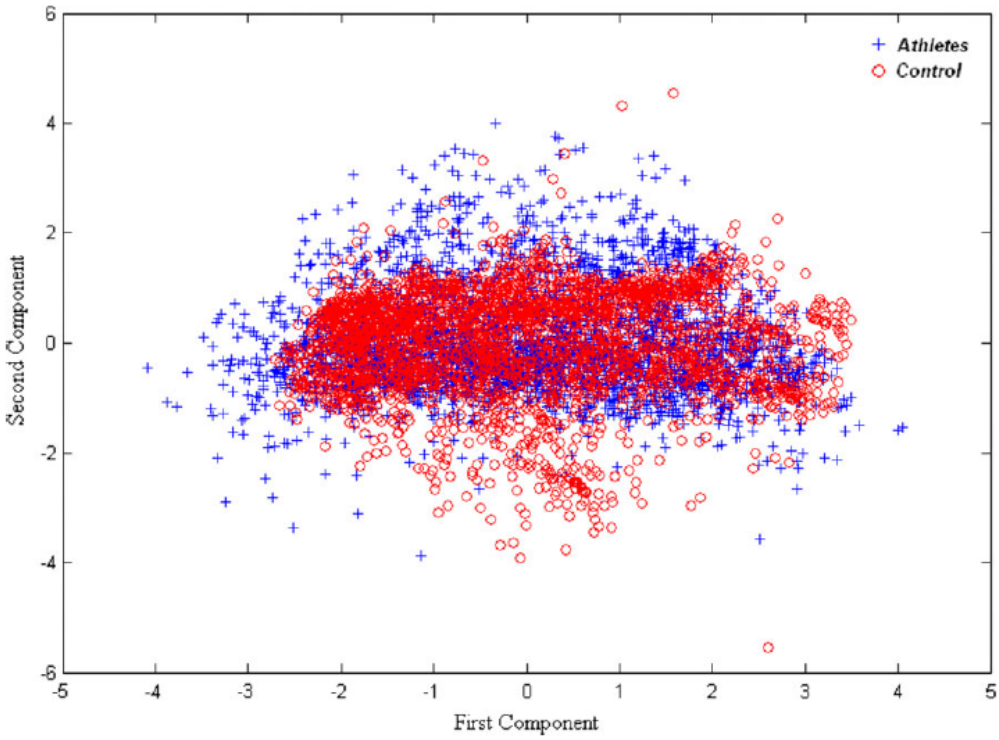

Fig. 3 PCA for ventilatory variability for both groups, the *x*-axis are the first component values and *y*-axis are the second component values

In the control group, the parameters change roles of importance. In this case, all parameters present almost the same contribution for the components value. It is necessary to register a more uniform dispersion around the zero. More specifically, the variance of the first and second component in PCA for the control group are 2.1137 and 0.85837. The third component assumes the value 0.027951. The first component is responsible for 70.5% of the total variance of the group followed by 28.6 and 0.9% from the second and third components, respectively. This fact promotes the result observed in Fig. 2, where data values distribution for the variance analysis through PCA shows a considerable number of points out of the boundary limits formed by the vectors VE, Vt, and FR. The vectors are a projection of three independent components in a two-dimensional space. The coordinates of each vector in Fig. 2 are VE = (0.6826, −0.0159); Vt = (0.5386, −0.6647); and FR = (0.4938, 0.7469) where the first value corresponds to the *x*-axis and the second value to the *y*-axis.

Thus, the length of the vectors that represents the variables Ve, Vt, and FR defines their contribution for the data dispersion. Note that, the FR and Vt are perpendicular in Figs. 1 and 2, this fact is resulted from the physiological meaning of Ve, which is the composition of these two measures. In Fig. 1, the vector Vt has the length bigger than the vector FR resulting in a higher contribution for the variation of Ve parameter. In Fig. 2 the roles are inverted, the length of the vector FR is bigger when compared with Vt length.

Figure 3 shows the PCA in two-dimensional space, this figure was generated from the union of the two first components figures, calculated separately, but designed in a single graph. In this case, it is possible to re-affirm that the VE, Vt, and FR dispersion is significantly higher in the control group, which is resulted from the values obtained in PCA. This result is expected but not easily observed. The PCA promotes a better level of understanding data dispersion. In this case, the control group presents higher global variability than the athletes group.

This cannot be statistically observed if the analysis is based on simple statistical procedure, as an example, in the box plots showed on Fig. 4. This figure show small differences between groups and the inversion of roles from the variables Vt and FR cannot be noted. The global analysis through PCA provides a general pattern's overview of the variables and its role for the group global dispersion.

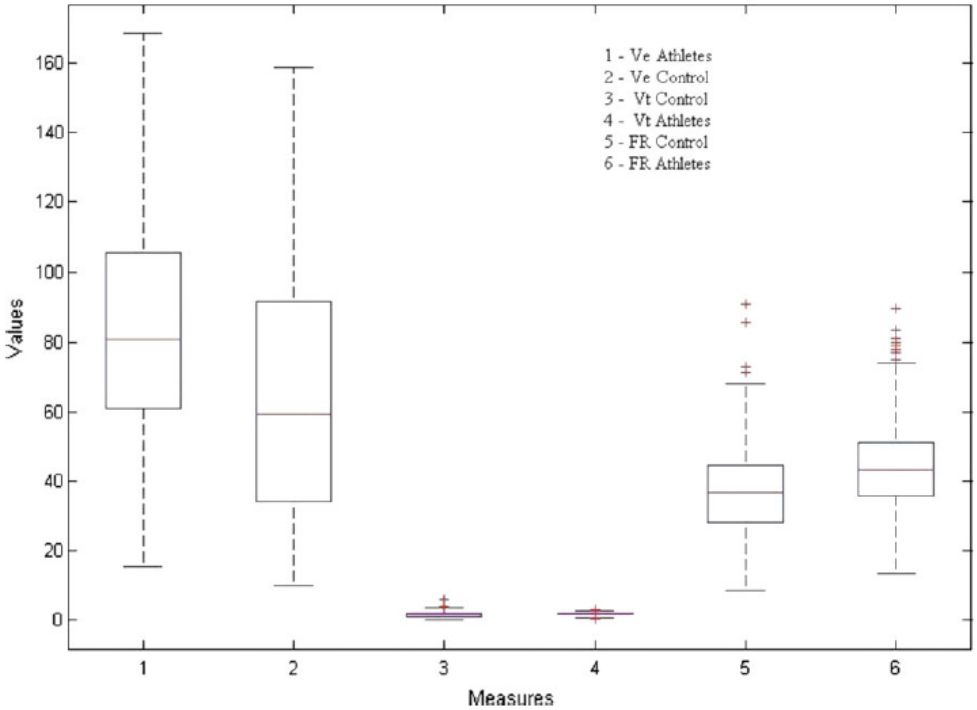

Fig. 4 Boxplot for the Ve, Vt, and RR values for two groups

4 Discussion

The response analysis of different biological parameters to exercise allows the precocious diagnosis of different pathological conditions. In this context, the excessive variability of ventilation parameters during exercise (periodic breathing) confers worst prognosis to patients with heart failure, regardless the presence of other classic prognostic parameters [10]. Periodic breathing seems to be the abnormal extreme of a more insidious process characterized by the inability of feedback loops to keep ventilation parameters varying around an accepted set point [3].

In fact, a myriad of abnormal ventilator variability responses during exercise seems to exist between normal pattern and periodic breathing [1, 2, 4]. During a progressive maximal exercise test, Vt, FR and thus, VE increase from rest to peak exercise. At low exercise intensity, the increase in VE is primarily accomplished by an increase in VE, while in more intense exercise the increase in FR is usually responsible for increases in VE [2, 9].

The variability of VE in athletes is secondary to a more pronounced variability in Vt, whereas in sedentary men the variability of FR seems to be the responsible for VE variability during exercise. These results could only be obtained due to the implementation of PCA, allowing a better understanding on how Vt and respiratory vary and interact in order to interfere in VE variability in sedentary and trained men during a maximal progressive cardiopulmonary exercise test and showing the roles of the variables on exercise in two distinct groups.

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3.4 **Time-domain ventilatory variability is higher in sedentary than athlete men during a maximal exercise test**

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Abstract

Background: The occurrence of minute-ventilation oscillations during exercise, named periodic breathing, exhibits important prognostic information in patients with heart failure. The adaptability of ventilatory variability to physical training is still unknown, but we have recently reported the reversal of periodic breathing after cardiac rehabilitation in a patient with heart failure. Considering that exercise training could influence the fluctuation of ventilatory components during exercise, we hypothesized that ventilatory variability during exercise would be greater in sedentary men than athletes.

Objective: Compare time-domain variability of ventilatory components of sedentary healthy men and athletes during a progressive maximal exercise test, evaluating its correlation to variables usually obtained during a cardiopulmonary exercise test.

Methods: Analysis of time-domain variability (SD/n and RMSSD/n) of minute-ventilation (Ve), respiratory rate (RR) and tidal volume (Vt) during a maximal cardiopulmonary exercise test of 9 athletes and 9 sedentary men. Statistical analysis: paired bicaudal Student T test and Pearson´s correlations test.

Results: Sedentary men exhibited greater variability of Vt (SD/n ($x10^3$): 1.6±0.1 vs. 0.9±0.1 l/min/breath; $p<0.001$) and V_E [SD/n ($x10^3$): 97.5±7.7 vs. 71.6±1.6 l/breath; $p= 0.038$) than athletes. VE/VCO_2 correlated to Vt variability (RMSSD/n) in both groups ($p=0.003$).

Conclusions: Time-domain variability Vt and V_E during exercise is greater in sedentary than athletes, with a positive relationship between VE/VCO_2 pointing to a possible influence of ventilation-perfusion relationship on ventilatory variability during exercise in healthy volunteers.

Key words: Ventilatory variability, cardiopulmonary exercise test, athlete

Introduction

Respiratory dysfunction is present in a myriad of different diseases, not only the ones directly affecting the lungs. In this setting, patients with sleep apnea or heart failure usually exhibit a certain degree of respiratory malfunctioning [1, 2]. Even when lung function impairment is absent during rest, there may be abnormalities in ventilatory responses during exercise in patients with heart failure.

The occurrence of minute-ventilation oscillations during exercise, named periodic breathing, exhibits important prognostic information in patients with heart failure [3, 4]. There are some concerns that deserve discussion and currently impair the widespread use of minute-ventilation oscillations in the evaluation of heart failure patients. First of all, there is no universally accepted definition of periodic breathing [5, 6]. Actually, the presence of periodic breathing is a powerful predictor of adverse outcome which prevalence varies from 25 to 31% of heart failure patients, depending on the criteria used to define it [5]. Some patients exhibit ventilatory oscillations during exercise without complying to any proposed criteria of periodic breathing and the magnitude of these oscillations (ventilatory variability) inversely correlates to left ventricular ejection fraction in heart failure [7].

Different cardiopulmonary variables exhibit some adaptation to physical training. In fact, exercise training confers adaptations that are capable of altering not only rest ventilatory parameters, but also their responses to a single exercise section. The adaptability of ventilatory variability to physical training is still unknown, but we have recently reported the reversal of periodic breathing after 14 weeks of cardiac rehabilitation in a patient with heart failure [8].

Considering that exercise training could influence the fluctuation of ventilatory components during exercise, we hypothesized that ventilatory variability during exercise would be greater in sedentary men than athletes. Thus, the present study was designed to compare time-domain variability of ventilatory components of sedentary healthy men and athletes during a progressive maximal exercise test, evaluating its correlation to variables usually obtained during a cardiopulmonary exercise test.

Methods

Volunteers

Eighteen male volunteers (9 sedentary and 9 athletes) were invited to participate in the study. All of them were considered healthy after anamnesis and physical examination. None of them were smokers or had been in regular use of any kind of medication. Sedentary men were not involved in any regular physical activity. Athletes were professional soccer players from the same soccer team in Rio de Janeiro, Brazil.

Study protocol

All volunteers provided written informed consent to participate in the study after full explanation of the procedures and their potential risks. The investigation conformed to the principles outlined in the Declaration of Helsinki and have been approved by the Institutional Research Ethics Committee on Human Research.

The groups performed a maximal cardiopulmonary exercise test in a treadmill (Trackmaster 30x30, USA) following an individualized ramp protocol. Exercise test was interrupted whenever the perceived exertion reached grade 10 in a modified BORG scale. Cardiopulmonary exercise tests were performed with gas exchange and ventilatory variables being analyzed breath-by-breath using a calibrated computer-based exercise system (Ultima CardiO2 System, Medical Graphics Corporation, USA). The O_2 and CO_2 analyzers were calibrated before each test using a reference gas (12% O_2; 5% CO_2; nitrogen balance). The pneumotachograph used was also calibrated, with a 3L syringe using different flow profiles. During each cardiopulmonary exercise test, a 12-lead electrocardiogram was continuously recorded (Cardioperfect, Welch Allin, USA) and heart rate automatically registered. Oxygen consumption (VO_2); carbon dioxide production (CO_2), tidal volume (Vt) and respiratory rate (RR), were registered breath-by-breath. Minute ventilation (VE), O_2 and CO_2 ventilatory equivalents (VE/VO_2 and VE/VCO_2) were automatically calculated (Breeze Software 6.4.1, Medical Graphics, USA).

Standard deviation (SD) and root mean square successive difference (RMSSD) of VE, RR and Vt during exercise test were calculated for each patient. Patients have exercised until exhaustion. Time to exhaustion was not the same for all patients. Considering that the number of observations has a direct influence on variability measurement, we normalized variability (SD and RMSSD) by the number

of respiratory cycles, reducing the probability that variability could be greater due solely to a greater number of observations registered in longer tests (SD/n and RMSSD/n, respectively) [7].

Statistical analysis

Statistical analysis was performed using the software Statistica 7.0 (Statsoft Inc, USA). Variables from the cardiopulmonary exercise tests showed normal distribution when analyzed by the Shapiro Wilk's W test. Exercise variables in both groups were compared by paired bicaudal Student T test. As there were differences between athlete and sedentary data (see table 1), Pearson´s correlations were separately assessed for each group. Significance was set at $p < 0.05$. Results are presented as mean ± SE.

Results

The demographic and anthropometric characteristics of both groups are described in table 1. All tests were considered maximal and reached a respiratory quotient greater than 1.10 (athletes: 1.34 ± 0.01; sedentary: 1.29 ± 0.13; p=0.38). Peak cardiopulmonary exercise data of both groups are shown in table 2.

Table 1 Demographic and anthropometric data of volunteers (n=18).

Variable	Sedentary (n=9)			Athete (n=9)			P value*
Age (years)	26	±	6	22	±	2	0.128
Weight (kg)	77.7	±	11.0	70.6	±	1.3	0.134
Height (m)	1.75	±	0.06	1.75	±	0.03	0.866
BMI (kg/m2)	25.4	±	3.04	23.05	±	1.14	0.064

*Comparison between groups by student T test.

Table 2. Peak exercise data during graded maximal cardiopulmonary exercise test performed by athletes and sedentary men in a treadmill.

	Athletes (n=9)	Sedentary men (n=9)	*P* value
VO_2 (mL/kg/min)	47.8 ± 0.1	42.6 ± 1.4	0.029
VCO_2 (mL/kg/min)	74.8 ± 0.9	46.1 ± 2.2	<0.001
Ve (L/min)	128.7 ± 0.1	123.4 ± 4.9	0.550
Respiratory rate (breaths/min)	57 ± 1	54 ± 2	0.540
Vt (L)	2.3 ± 0.0	2.3 ± 0.1	0.837
Heart rate (beats/min)	181 ± 1	186 ± 2	0.343
VE/VO_2	2.7 ± 0.0	2.9 ± 0.1	0.309
VE/VCO_2	1.8 ± 0.0	2.8 ± 0.2	0.003
RR/VO_2 (breaths/ml/Kg/min)	1.2 ± 0.0	1.3 ± 0.1	0.363
VO_2/HR (ml/ beat)	0.3 ± 0.0	0.2 ± 0.0	0.015

VO_2: Peak oxygen consumption; VCO_2: peak carbon dioxide production; Ve: minute-ventilation; Vt: tidal volume.

P value refers to the result of paired student's T test

There was no difference between the number of breaths during exercise test for each group (athletes: 384±1 vs. sedentary: 345±16 breaths/test). Sedentary men exhibited higher time-domain variability of minute ventilation and tidal volume than athletes during cardiopulmonary exercise test, as showed in table 3.

Table 3 Time domain ventilatory variability of respiratory rate (RR), tidal volume (Vt) and minute ventilation (VE) during maximal exercise test performed by athletes and sedentary men.

Variable ($x10^3$)	**Athletes (n=9)**	**Sedentary (n=9)**	***P* value***
Respiratory rate			
SD/n ($breath^2$/min)	27,7 ± 0,4	31,3 ± 2,0	0,281
RMSSD/n ($breath^2$/min)	20,3 ± 0,1	19,7 ± 0,7	0,690
Tidal volume			
SD/n (l/min/breath)	0,9 ± 0,0	1,6 ± 0,1	<0,001
RMSSD/n (l/min/breath)	1,0 ± 0,0	1,2 ± 0,1	0,102
Minute-ventilation			
SD/n (l/breath)	71,6 ± 1,6	97,5 ± 7,7	0,038
RMSSD/n (l/breath)	35,9 ± 1,8	34,9 ± 3,0	0,833

*Comparison between groups by student T test.

As shown in tables 4 and 5, VE/VCO_2 was correlated to tidal volume variability (RMSSD/n) during exercise test both in athletes and sedentary men. There was no other correlation between peak cardiopulmonary data and time-domain ventilatory variability throughout maximal exercise test in any group.

Table 4: Bivariate linear correlations between peak cardiopulmonary exercise data and time-domain variability of ventilatory variables among athletes (n=9).

	Respiratory rate		**Tidal volume**		**Minute ventilation**	
	SD/n	RMSSD/n	SD/n	RMSSD/n	SD/n	RMSSD/n
VO_2	0.424	0.199	0.771	0.206	0.201	0.642
VCO_2	-0.347	0.204	-0.497	-0.531	-0.561	-0.491
Heart rate	0.513	0.340	0.414	0.278	0.539	0.274
VE/VO_2	0.613	0.267	0.467	0.612	0.382	0.511
VE/VCO_2	0.471	0.250	0.604	0.854*	0.665	0.665
VO_2/HR	-0.181	0.246	0.006	-0.195	-0.207	0.190

*P=0.003

Table 5: Bivariate linear correlations between peak cardiopulmonary exercise data and time-domain variability of ventilatory variables among sedentary men (n=9).

	Respiratory rate		**Tidal volume**		**Minute ventilation**	
	SD/n	RMSSD/n	SD/n	RMSSD/n	SD/n	RMSSD/n
VO_2	0.425	0.200	0.077	0.206	0.201	0.642
VCO_2	-0.347	-0.204	-0.496	-0.531	-0.561	-0.491
Heart rate	0.513	0.340	0.414	0.278	0.539	0.274
VE/VO_2	0.613	0.267	0.467	0.612	0.382	0.512
VE/VCO_2	0.471	0.250	0.604	0.855*	0.665	0.665
VO_2/HR	0.232	0.072	-0.085	0.086	-0.005	-0.053

*P=0.003

Discussion

The presence of abnormal oscillations of minute ventilation during exercise test, named periodic breathing, indicates bad prognosis in heart failure, regardless the presence of other classic prognostic parameters [3, 4]. Unfortunately, there is

disagreement regarding the criteria that should be used to detect this phenomenon [5]. Some patients exhibit minute-ventilation oscillations during exercise which does not appear to be normal neither comply to established criteria of periodic breathing [8]. In fact, Periodic breathing seems to be the abnormal extreme of a more insidious process characterized by the inability of feedback loops to keep ventilatory parameters varying around an accepted set point. Thus, a method that enables quantitative evaluation of oscillatory breathing during exercise would be useful in clinical setting. We have previously applied time-domain variability techniques to evaluate patients with heart failure and found that ventilatory variability during a maximal exercise test inversely correlates to left ventricle ejection fraction [7]. Although this information is clinically relevant, there are some clinical questions that remain to be answered before time-domain ventilatory variability can be incorporated in clinical practice.

Considering that most ventilatory parameters exhibit some adaptation to physical training, it is conceivable to hypothesize that ventilatory variability would also be affected by chronic exposure to physical exercise. The present study compared ventilatory variability throughout exercise in athletes and sedentary men and concluded that untrained volunteers exhibited greater time-domain variability of minute-ventilation and tidal volume than trained ones. Interestingly, tidal volume variability (RMSSD/n) was positively correlated to VE/VCO_2 in both athletes and sedentary men. Peak VE/VCO_2 is an indirect indicator of either exercise hyperventilation or ventilation-perfusion mismatch. Considering that there was no difference between peak respiratory rate in both groups, it seems that the higher VE/VCO_2 found in sedentary men indicates a worst, although not abnormal, ventilation-perfusion relationship when these volunteers are compared to athletes.

It is important to note that all volunteers were healthy and without any cardiovascular or respiratory disease. Therefore, mechanisms involved in Cheyne-Stokes respiration and periodic breathing, such as hypocapnia, increased central and peripheral chemosensitivity [9] and pulmonary blood flow fluctuations [10], which are considered key mechanisms of periodic breathing in heart failure, would probably not be useful in understanding physiological ventilatory variability during exercise in healthy subjects. VE/VCO_2 was the only cardiopulmonary variable correlated to ventilatory variability in the present study. Although it was not designed to evaluate the mechanisms that influence ventilatory variability during exercise, this finding

points to a possible involvement of ventilation-perfusion mismatch in the genesis of tidal volume variability during exercise.

Study limitations

Some operational and technical aspects could have influenced the results of the present study. Subjects were not submitted to rest pulmonary function tests before entering the study. Considering none of them had any past history of pulmonary disease or smoking, the absence of rest pulmonary function tests, although desirable, does not seem to be a major issue influencing the present results.

All breath-by-breath data was collected by a face mask. Thus, the use of face mask could not explain the different results when both groups were compared. The use of different interfaces to breath analysis may influence the depth and rate of breathing [11]. Although this effect appears to be restricted to lower levels of exercise [12], it seems reasonable not to interchangeably compare ventilatory variability results recorded using mask, mouthpiece or canopy.

Finally, this is a transversal study where trained and untrained men were compared. A study that evaluates the effects of physical training would rather have a longitudinal than a transversal design. Nevertheless, the only difference between both studied groups was their peak VO_2, which was higher in athletes. Thus, although athletes were not longitudinally evaluated, it seems that the different exercise responses in both groups could be attributable to physical training.

Conclusions

Time-domain variability of minute ventilation and tidal volume during exercise is higher in sedentary than athletes. There is positive relationship between VE/VCO_2 and tidal volume variability during exercise, pointing to a possible influence of ventilation-perfusion relationship on ventilatory variability during exercise in healthy volunteers. The exact mechanisms that influence ventilatory variability during exercise remain to be studied.

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3.5 **Physical training reduces time-domain ventilatory variability during exercise in healthy individuals: a randomized trial**

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Abstract

Introduction: Sedentary men exhibit higher time-domain ventilatory variability during maximal exercise when compared to athletes. However, as an evidence from cross-sectional study, it is unknown whether this is an effect of exercise training itself or a result from a selection bias.

Objective: To evaluate the effects of physical training on time-domain ventilatory variability during dynamic exercise in healthy subjects.

Methods: Randomized controlled trial where time-domain ventilatory variability during exercise was evaluated in 24 healthy individuals before and after 12 weeks of exercise training (Exercise group, n=12) or no intervention (control group, n=12).

Results: After 12 weeks, time-domain variability of respiratory rate was higher in the control group when compared to exercise group. Exercise training reduced respiratory rate and tidal volume variabilities (RMSSD/n).

Conclusion: Exercise training reduced time-domain ventilatory variability of healthy individuals during a maximal exercise test. The impact of this adaptation remains to be evaluated.

Key words: Exercise training, ventilatory variability, cardiopulmonary exercise test, respiratory frequency

Introduction

Exercise periodic breathing is characterized by the regular alteration of tidal volume with a crescendo-decrescendo pattern without interposed apnea, throughout a maximal exercise test, (1-4). Interest in the pathophysiological basis and clinical significance of exercise periodic breathing has increased in view of the evidence of its prognostic value (1, 2, 5).

The absence of a universally accepted definition of this phenomenon impairs its widespread use in clinical practice (3, 6). Considering that patients may exhibit ventilatory fluctuations during exercise test, without complying to any established criteria of periodic breathing, a method that enables quantification of these fluctuations would probably be useful in clinical practice. We have previously proposed the application of time-domain variability techniques to quantify ventilatory oscillations during exercise. Actually, ventilatory variability inversely correlates to left ventricle ejection fraction in heart failure patients (7). We have also found that sedentary men exhibit higher ventilatory variability during maximal exercise test when compared to athletes (8). However, as an evidence from cross-sectional study, it is unknown whether this is an effect of exercise training itself or a result from a selection bias.

Few studies have investigated strategies to reverse exercise periodic breathing. Ribeiro et al (9) found that milrinone reduced the incidence of exercise periodic breathing in heart failure patients. Respiratory muscle training program reduced the incidence of ventilatory oscillations during maximal exercise test in patients with heart failure (10). More recently, we have published a case report where exercise periodic breathing was reversed after 4 months of cardiac rehabilitation (7).

In healthy individuals, the effects of exercise training in time-domain ventilatory variability during exercise are not known. We have hypothesized that exercise training would reduce time-domain ventilatory variability during a maximal exercise test in these subjects. Thus, this study was designed to evaluate the effects of exercise training in time-domain ventilatory variability in healthy subjects.

Methods

Sample

Twenty four healthy individuals were invited to participate in the study. The eligibility for taking part in the study was verified through a clinical history assessment, physical examination, biochemical blood analyses, resting electrocardiogram and maximal cardiopulmonary exercise testing. All the individuals fulfilled the following criteria: age between 18 and 40 years, women had regular menstrual cycles, no chronic disease and no recent infections, body mass index (BMI) between 18.5 and 29.9 $kg.m^{-2}$, systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg, blood glucose < 100 $mg.dL^{-1}$, total cholesterol < 239 $mg.dL^{-1}$, low density lipoprotein < 159 $mg.dL^{-1}$, triglycerides < 200 $mg.dL^{-1}$, no regular use of medications, except oral contraceptives, normal resting and exercise electrocardiogram, and sedentarism (not engaged in exercise activities lasting 30 min or more, 3 times per week during the last three months). The study procedures were approved by the Ethics Committee of Antonio Pedro University Hospital, and written informed consent was obtained from all participants prior to the experimental procedures.

Study design

Cardiopulmonary exercise tests were performed by each volunteer before and after a 12 week period of exercise training (exercise group, n=12) or no intervention

(control group, n=12). All tests were done in the morning, an hour after a standardized light breakfast. Women were evaluated from the 1st until the 12th day after the onset of menstruation. Individuals did not drink alcohol or caffeinated beverages and did not perform intense physical activity for at least 24 h before the assessment. In addition, they slept well the night prior to the tests. Individuals were randomly assigned to be in the intervention group (exercise training) or the control group.

Cardiopulmonary Exercise Test

Cardiopulmonary exercise test was performed on a treadmill (Super ATL, Inbramed, Porto Alegre, RS, Brazil). Before the test warm-up (walk at 3 km/h; 0% grade for three minutes) were performed. The test followed an individualized ramp protocol (11) until exhaustion, followed by a five minute recovery period at 4 km/h and 0% grade. Individuals were verbally encouraged to exercise until exhaustion.

Cardiopulmonary exercise tests were performed with gas exchange and ventilatory variables being analyzed breath-by-breath using a calibrated computer-based exercise system (Ultima CardiO2 System, Medical Graphics Corporation, USA). The O_2 and CO_2 analyzers were calibrated before each test using a reference gas (12% O_2; 5% CO_2; nitrogen balance). The pneumotachograph used was also calibrated, with a 3L syringe using different flow profiles. During each cardiopulmonary exercise test, a 12-lead electrocardiogram was continuously recorded (Cardioperfect, Welch Allin, USA) and heart rate automatically registered. Oxygen consumption (VO_2); carbon dioxide output (CO_2), tidal volume (Vt) and respiratory rate (RR), were registered breath-by-breath. Minute-ventilation (VE), O_2 and CO_2 ventilatory equivalents (VE/VO_2 and VE/VCO_2) were automatically calculated (Breeze Software 6.4.1, Medical Graphics, USA).

Standard deviation (SD) and root mean square of successive differences (RMSSD) of VE, RR and Vt during exercise test were calculated for each patient. Considering that it is not feasible that all volunteers reach peak exercise at the same time, time to exhaustion was not the same for all patients. Considering that the number of observations has a direct influence on variability measurement, variability (SD and RMSSD) was normalized by the number of respiratory cycles, reducing the probability that variability could be greater due solely to a greater number of observations registered in longer tests (SD/n and RMSSD/n, respectively) (12).

Muscular Strength Evaluation

The muscular strength was measured by the maximum load test, using Kraemer and Fry's protocol(13). Prior to the test, the correct execution of each exercise was demonstrated in order to avoid errors in execution during the test. The subjects performed a specific warm-up (50% of the maximum load) for the first exercise of the upper (bench press) and lower (leg extension) parts of the body. To determine the maximum load, the individuals had three to five attempts, at intervals ranging from 3-5 min. If the participant performed two repetitions with the estimated load, the weight was increased for the next attempt, and if the participant could not perform a full repetition, the load was them reduced.

Exercise Training Protocol

Supervised exercise training was performed three times a week over 12 weeks by individuals assigned to the intervention group. Each session consisted of five minutes of warm-up with stretching exercises, ten minutes of aerobic exercise performed on a treadmill, 15 minutes of resistance exercises performed on a multistation resistance machine (bench press, leg extension, lat pulldown and plantar flexion), ten minutes of aerobic exercise on a cycle ergometer, 15 minutes of

resistance exercise in multistation resistance machine (shoulder press, sit-ups and knee flexion), ten minutes of aerobic exercise on a treadmill and five minutes of recovery with stretching exercises. Intensities of both aerobic and resistance exercises was adjusted every two weeks. Aerobic exercise was prescribed accordingly to the anaerobic threshold heart rate (ATHR): in the first week: 90% ATHR and in the last week 115% ATHR. Resistance exercises started at 40% and ended at 85% of 1-RM, and 3 sets of 10 repetitions were performed for each exercise.

Dietary Protocol

Individuals filled out records of food consumption on 3 alternate days (one of these was at a weekend), within an interval of 7 days. After analysis of food records, all subjects were instructed to follow a feeding pattern, individually designed by a dietitian, in order to promote dietary re-education (well-balanced protein, carbohydrate, fat, vitamins and minerals). In addition, individuals that were overweight (body mass index between 25 and 29.9 kg/m^2) followed a hypocaloric diet, which was individualized to reduce body weight by 7%. Body weight was measured every week to verify compliance to diet.

Statistical Analysis

The Shapiro-Wilk and the Levene tests were used to verify the distribution and homogeneity of variances of the variables, respectively. Groups' characteristics and deltas (after-before) values were compared using two-tailed paired Student´s t-test. Groups' characteristics before and after the intervention (exercise training) were compared using two-way ANOVA [factors: group (intervention *vs*. control) and time (before-intervention *vs.* after-intervention)] followed by the Fisher Exact post hoc test. As there were differences between groups (see results section), bivariate linear

correlation coefficients between changes in ventilatory variability and changes in peak VO_2, weight and body mass index were separately calculated for each group. Statistical significance was considered for $P \leq 0.05$. All analyses were performed with STATISTICA© software (version 7.0, StatSoft, Inc., Tulsa, OK, USA).

RESULTS

Twenty-four volunteers were included in the study and their anthropometric characteristics are displayed in table 1.

Table 1. Demographic and anthropometric data of volunteers submitted to exercise training (exercise group) or no intervention (control group).

Variable	Exercise group (n=12)	Control group (n=12)	*P**
Men: women	2:10	2:10	1.00
Age (years)	36 ± 2	30 ± 2	0.07
Weight (kg)	68.8 ± 2.5	72.4 ± 2.3	0.31
Height (m)	1.66 ± 0.02	1.67 ± 0.02	0.70
Body mass index (kg/m2)	25.01 ± 0.80	26.0 ± 0.66	0.36
Peak VO_2 (ml/kg/min)	28.7 ± 1.8	29.5 ± 1.2	0.70

**P*= Comparison between groups by two-tailed Student´s T test

After 12 weeks, volunteers in the exercise group presented higher peak VO_2 (37.12±2.51 vs. 25.9±1.46, $P<0.001$) and lower body mass index (23.39±0.70 vs. 26.32±0.70, $P=0.008$) than individuals in control group. In addition, time-domain variability of respiratory rate during exercise was higher in the control group when compared to volunteers in the exercise group (table 2). The calculation of deltas (after-before 12 weeks) not only corroborated, but also expanded this finding, showing that exercise training reduced respiratory rate and tidal volume ventilatory variabilities (RMSSD/n) during exercise, as showed in figure 1.

Table 2. Time-domain variability of respiratory variables before and twelve weeks after exercise training (exercise group) or no intervention (control group)

Variable ($x10^3$)	Intervention group (n=12)		Control group (n=12)	
	before	after	before	After
Vt SD/n (l/min/breath)	1.2 ± 0.1	1.4 ± 0.1	1.3 ± 0.1	1.3 ± 0.1
Vt RMSSD/n (l/min/breath)	1.0 ± 0.1	0.9 ± 0.1	1.0 ± 0.1	1.1 ± 0.1
RR SD/n ($breath^2$/min)	32.3 ± 2.2	31.5 ± 3.0	31.2 ± 2.9	35.4 ± 4.2
RR RMSSD/n ($breath^2$/min)	21.5 ± 1.8	18.2 ± 2.0	21.9 ± 2.2	25.0 ± 2.9*
VE SD/n (l/breath)	64.8 ± 5.1	77.7 ± 8.1	69.0 ± 6.8	70.1 ± 7.2
VE RMSSD/n (l/breath)	22.9 ± 1.7	24.7 ± 2.5	27.8 ± 3.4	30.9 ± 4.2

*P= 0.04 vs intervention group, same moment

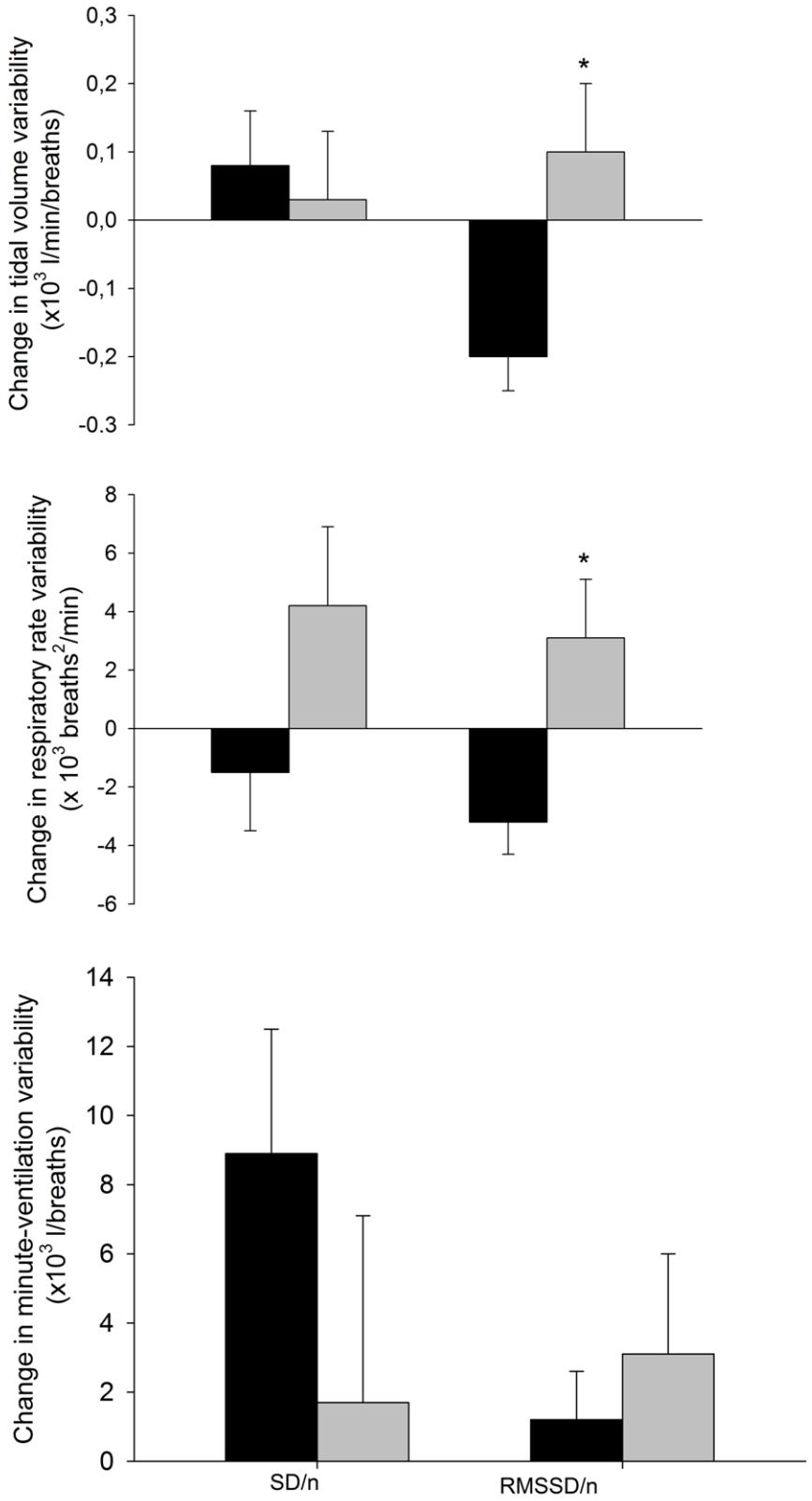

Figure 1. Changes of time domain variability (SD/n and RMSSD/n) of tidal volume, respiratory rate, and minute ventilation during exercise after twelve weeks of physical training (exercise group-black bars) or no intervention (control group- gray bars). *P< 0.02 vs. intervention group

Correlations between the 12-weeks´ changes in exercise ventilatory variability indexes and changes in anthropometrical data and peak VO_2 were separetlety accessed in each group of volunteers. As can be seen in tables 3 and 4, there was no correlation between these variables in control group, but in exercise group, the change in tidal volume RMSSD/n has showed significant correlation with changes in body weight and body mass index.

Table 3. Linear correlations between changes in anthropometrical and peak exercise data and changes in time-domain ventilatory variability after 12 weeks of exercise training (n=12).

	Respiratory rate		Tidal volume		Minute ventilation	
	SD/n (Δ)	RMSSD/n (Δ)	SD/n (Δ)	RMSSD/n (Δ)	SD/n (Δ)	RMSSD/n (Δ)
Peak VO_2 (Δ)	-0.527	-0.392	0.331	-0.127	0.226	0.344
Weight (Δ)	0.244	0.321	0.207	0.690*	0.171	0.126
Body mass index(Δ)	0.204	0.343	0.181	0.675*	0.134	0.149

*$P<0.02$

Table 4. Linear correlations between changes in anthropometrical and peak exercise data and changes in time-domain ventilatory variability after 12 weeks of no intervention in control group (n=12).

	Respiratory rate		Tidal volume		Minute ventilation	
	SD/n (Δ)	RMSSD/n (Δ)	SD/n (Δ)	RMSSD/n (Δ)	SD/n (Δ)	RMSSD/n (Δ)
Peak VO_2 (Δ)	0.167	0.102	0.187	0.360	0.388	0.347
Weight (Δ)	-0.003	-0.256	-0.293	-0.540	0.056	-0.127
Body mass index(Δ)	-0.030	-0.249	-0.289	-0.551	0.047	-0.165

DISCUSSION

Instability of breathing control due to heart failure manifests as exercise periodic breathing (14). Frequency of exercise periodic breathing has been reported to range from 12 to 30% of ambulatory heart failure patients managed at tertiary centers (1, 2). Olson et al (4) found that exercise periodic breathing may occur even in patients with heart failure with left ventricle ejection fraction higher than 40%. There is no doubt about the correlation between presence of ventilatory periodic

breathing and bad prognosis in heart failure patients, independently of left ventricle ejection fraction (5, 6).

Although the quantification of ventilatory oscillations is being extensively investigated in heart failure, little is known about this theme in healthy individuals. We have previously found that ventilatory variability during a maximal exercise test is higher in sedentary than athlete men (8) and that exercise variability of respiratory rate and tidal volume are different when athletes and sedentary are compared. As this information resulted from transversal observations, there were doubts regarding the real effects of physical training in exercise ventilatory variability. Thus, this is the first study to demonstrate that exercise training can reduce ventilatory variability in healthy sedentary subjects.

Actually, few studies have evaluated strategies to reverse the presence of ventilatory oscillations, and all of them have focused in heart failure. Oscillatory ventilation indexes are reduced after aerobic training in heart failure patients(10). Recently, Winkelmann et al (15) expanded these findings and reported additional improvements in oscillatory ventilation indexes when inspiratory muscle training was added to regular aerobic training in heart failure patients with respiratory muscle weakness.

Regarding patients with documented periodic ventilation, Ribeiro et al (9) have previously found that ventilatory periodic breathing can be reverted with milrinone or cardiac transplantation. More recently, we have published a case report where ventilatory periodic breathing was reverted after 12 weeks of cardiac rehabilitation in a patient with heart failure (7). Zurek et al (16) corroborated this finding and documented reduction of periodic breathing by regular physical training in heart failure patients.

In exercise group the 12-week change in tidal volume exercise variability was correlated to changes in body weight and body mass index. There was no correlation between changes in ventilatory variability and peak VO_2 change after 12 weeks of exercise training. In morbid obese individuals, excessive body weight can induce chest wall restriction (17) and loosing body weight may improve lung function (18). Nevertheless, considering that none of the individuals included in the study were even obese, this seems not to be the reason why ventilatory variability diminishes with body weight lost. Although we have not evaluated inspiratory capacity, it could have been improved by exercise training, and influenced the time-domain ventilatory variability during exercise in trained individuals.

Study limitations

We have not performed lung function tests in the subjects of the study. Although none of them reported any actual or previous lung disease, lung function would preferably have been evaluated. Considering that each individual was their control during the follow-up, the absence of lung function tests should not have influenced the present results.

CONCLUSION

Exercise training reduced time-domain ventilatory variability of healthy individuals during a maximal exercise test. The impact of this adaptation remains to be evaluated.

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3.6 **Reversal of periodic breathing after aerobic training in heart failure**

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CORRESPONDENCE

Reversal of periodic breathing after aerobic training in heart failure

A 58-yr-old male was referred for participation in a cardiac rehabilitation programme. He had a long-term history of hypertensive cardiomyopathy and systolic dysfunction and was clinically stable, being treated with β-blocker carvedilol, losartan, digitalis, diuretics and spironolactone, with no changes in medication in the previous 16 weeks. Echocardiogram showed a 17% left ventricular ejection fraction and the patient was in New York Heart Association Functional Class III.

Before starting the exercise training programme, the patient was submitted to a maximal progressive cardiopulmonary exercise test, on an electromagnetically braked cycle ergometer (Medifit 400L; Medical Fitness Equipment, Maarn, Netherlands), with work rate increments of 5 W every 1 min at 60 rpm until exhaustion. Oxygen uptake ($V'O_2$) and carbon dioxide production were determined by means of gas exchange on a breath-by-breath basis in a computerised system (SensorMedics; Vmax 229 model, BuenaVista, CA, USA). Peak oxygen consumption ($V'O_2$) was defined as the maximum attained $V'O_2$ at the end of the exercise period in which the patient could no longer maintain the cycle rate. During this test, patient showed a very low exercise capacity, with a peak $V'O_2$ of 9.3 $mL \cdot kg^{-1} \cdot min^{-1}$ and 35 W of peak power load. Evaluation of ventilation during exercise revealed the presence of periodic breathing (fig. 1), as identified by the criteria proposed by LEITE *et al.* [1] and others [2].

The patient underwent 4 months of exercise training, which consisted of 60-min exercise sessions 3 $times \cdot week^{-1}$ under medical supervision at the Heart Institute (affiliation) [3]. Each exercise session consisted of 5 min stretching exercises, 25 min cycling on an cycle ergometer in the first month and up to 40 min in the next 3 months, 10 min local strengthening exercises (sit-ups, push-ups and pull-ups) and 5 min of cool down with stretching exercises. The exercise intensity was established by heart-rate levels that corresponded to anaerobic threshold up to 10% below the respiratory compensation point obtained in the cardiopulmonary exercise test. When a training effect was observed, as indicated by the patients using a Borg perceived exertion scale, the cycle workload was slightly increased. Heart-rate reduction was rarely used to adjust the bicycle workload, since the patient was under β-blocker treatment. Aerobic exercise training duration increased progressively so that the patient could perform 40 min of bicycle exercise at the established intensity. Throughout the training period, medication was kept the same and no major clinical event occurred.

After 4 months of exercise training, left ventricular ejection fraction remained the same (17%), New York Heart Association Functional Class improved to II, and the patient was submitted to another cardiopulmonary exercise test, following the same exercise increment protocol and the same equipment used in the first evaluation. Peak results of both tests are presented in table 1. As noted in figure 1, maximal exercise time increased. Although the ventilation pattern in the second test still presented some oscillation, it was much closer to the expected physiological linear increase and thus, did not comply with the criteria for exercise periodic breathing [2].

RIBEIRO *et al.* [4] have shown reversal of periodic breathing with pharmacological intervention, more specifically, with milrinone or cardiac transplantation. To our knowledge, this is the first report of reversal of periodic breathing related to exercise training in a patient with chronic heart failure.

Periodic breathing seems to be related to mechanisms within central nervous system, more specifically with nuclei involved in respiratory control [5]. In addition, YAJIMA *et al.* [6] found that periodic breathing was consequent to fluctuations in pulmonary blood flow during exercise in heart failure patients. Although periodic breathing independently predicts cardiac mortality in heart failure patients [1], it is not a phenomenon directly correlated to low left-ventricular ejection fraction, as it could be suspected. For example, the occurrence of periodic breathing could predict cardiac mortality in patients who were waiting for cardiac transplantation, independent of ejection fraction. Indeed, in the present case report, left-ventricular ejection fraction and peak oxygen pulse (which is directly correlated to maximum cardiac output) remained the same, despite the improvements in peak $V'O_2$ and New York Heart Association Functional Class. Although the mechanisms involved in the development of periodic breathing are not completely understood, its role as a marker of worse prognosis in heart failure is well established. Thus, the reversal of periodic breathing after exercise training may have practical implications.

One could hypothesise that the non-occurrence of periodic breathing after exercise training could have happened by chance. Although a single case is not a strong enough evidence to exclude this possibility, it is important to notice that medication and clinical status were stable throughout exercise training period. In addition, CORRA *et al.* [7] have shown that occurrence of exercise periodic breathing is a reproducible breathing phenomenon; thus, it is very unlikely that the reversal of periodic breathing was not consequent to exercise training. Whether the reversal of periodic breathing after exercise training will occur in larger series of heart failure patients and if this reversal is related to prognosis improvement desires further investigation.

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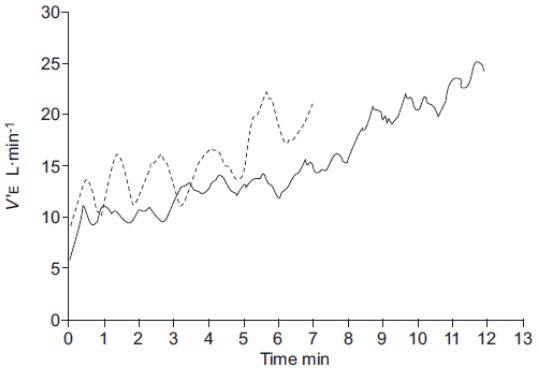

FIGURE 1. Ventilatory responses to graded cycle exercise of a patient with heart failure before (----) and after (——) four months of exercise training. V'_E: minute pulmonary ventilation.

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TABLE 1 Peak exercise data of a patient with heart failure before and after 4-month exercise training

Variable	Before	After
Time to exhaustion	7 min 00 s	11 min 46 s
$V'O_2$ mL·Kg^{-1}·min^{-1}	9.3	11.0
$V'CO_2$ mL·Kg^{-1}·min^{-1}	10.0	11.8
V'_E L·min^{-1}	24.3	27.2
Oxygen pulse	6.3	6.6
Power load W	35	60
Cardiac frequency beats·min^{-1}	101	115
Systolic blood pressure mmHg	160	180
Diastolic blood pressure mmHg	90	110

$V'O_2$: oxygen uptake; $V'CO_2$: carbon dioxide production; V'_E: minute ventilation.

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3.7 **Ventilation variabillity inversely correlates to ejection fraction in heart failure**

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LETTER

Ventilation variability inversely correlates to ejection fraction in heart failure

To the Editors:

Heart failure is currently considered a systemic disease. In this context, there is growing interest in cardiopulmonary interactions during rest, sleep and exercise [1]. Periodic breathing during exercise is characterised by regular waxing and waning of minute ventilation (V'_E) due to oscillations in central respiratory drive. Periodic breathing independently predicts mortality in heart failure patients [2], but is not directly correlated with low left ventricular ejection fraction. For example, the occurrence of periodic breathing could predict cardiac mortality in patients who were waiting for cardiac transplantation, independent of ejection fraction [2].

Clinical experience shows that some heart failure patients exhibit ventilatory oscillations during exercise testing without achieving the established criteria of periodic breathing (minimum of three regular oscillations; deviation of three consecutive cycle lengths within 20% of their average; and minimal ventilator oscillation of 5 L) [2]. We hypothesised that the analysis of time-domain variability of respiratory variables during exercise could add important clinical information, detecting changes of insufficient magnitude to be classified as periodic breathing. Cardiopulmonary exercise tests in 17 heart failure patients (53% male; mean±SD age 59±9 yrs; ejection fraction 23±6%) under standard treatment were retrospectively analysed following approval of the Institutional Ethics Committee. All maximal progressive cardiopulmonary exercise tests were performed on an electromagnetically braked cycle ergometer (Medifit 400L; Medical Fitness Equipment, Maarn, the Netherlands), with work-rate increments of 5 W every 1 min at 60 rpm until exhaustion. V'_E, respiratory frequency (f_R) and tidal volume (V_T) were registered on a breath-by-breath basis using a computerised system (Vmax 229; SensorMedics, Buena Vista, CA, USA). The SD and root mean square successive difference (RMSSD) of V'_E, f_R and V_T during exercise testing were calculated for each patient. Considering that the number of observations has a direct influence on measures of variability, and that patients had exercised until exhaustion and thus time to exhaustion was not the same for all patients, variability (SD and RMSSD) was normalised using the number of respiratory cycles, reducing the probability that variability could be greater due to a greater number of observations registered in longer tests (SD/n and RMSSD/n, respectively). A complete two-dimensional echocardiogram was obtained at rest. Left ventricular ejection fraction was calculated using a modified Simpson's biplane method.

Ejection fraction was inversely correlated with V'_E and f_R variability but not with V_T variability (table 1).

Although time-domain variability of breathing variables during rest has previously been used to predict success of weaning from mechanical ventilation [3], to our knowledge, this is the first time that this analysis has been applied to exercise data from heart failure patients. The present results show that patients with lower ejection fractions exhibit greater variability in V'_E and f_R throughout exercise testing. The calculations presented can be easily performed, and may add important clinical information in heart failure patients. Further studies evaluating the prognostic value of time-domain variability of V'_E and f_R during exercise are warranted.

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TABLE 1 Linear correlations between ejection fraction (EF) and time-domain variability of breathing variables during maximal cardiopulmonary exercise testing

		V'_E		V_T		f_R	
		SD/n	RMSSD/n	SD/n	RMSSD/n	SD/n	RMSSD/n
EF	R	-0.531	-0.511	-0.442	-0.452	-0.507	-0.510
	P	0.034	0.043	0.076	0.068	0.037	0.036

V'_E: minute ventilation; V_T: tidal volume; f_R: respiratory frequency; RMSSD: root mean square successive difference; n: number of breaths.

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4 **DISCUSSÃO**

Nesta tese apresentamos uma série de estudos sobre variabilidade da ventilação durante o exercício. Conforme já apresentado e amplamente discutido, a confirmação de que a presença de ventilação periódica durante o exercício confere pior prognóstico a pacientes com insuficiência cardíaca (3-5) aumentou o interesse da comunidade científica a respeito deste tema. A ventilação periódica caracteriza-se pela presença, durante o teste cardiopulmonar de exercício, de alterações regulares, do volume corrente com um padrão crescente-decrescente sem que ocorram períodos de apnéia (84).

Autores divergem a respeito dos critérios necessários para a identificação da ventilação periódica (75). Obviamente, o uso de diferentes critérios (4, 5) para identificação deste fenômeno pode alterar sua capacidade de inferir o prognóstico de pacientes. Mais especificamente, Ingle e colaboradores (75) compararam o impacto do uso dos dois principais grupos de critérios utilizados para identificar a ventilação periódica durante o exercício, em 240 pacientes com insuficiência cardíaca. O uso dos critérios de Corrá e colaboradores (5) identificou a presença de ventilação periódica em 25% dos pacientes avaliados. Quando o critério sugerido por Leite e colaboradores (4) foi utilizado, 31% dos pacientes do mesmo grupo teve diagnóstico de ventilação periódica durante o teste cardiopulmonar de exercício. Apesar da escolha do critério para identificação da ventilação periódica durante exercício ter influenciado a capacidade de detecção e, conseqüentemente a incidência do fenômeno na população estudada, ambos os métodos apresentaram sensibilidade e especificidade semelhantes para o risco de mortalidade em um ano (75).

A combinação dos critérios sugeridos por Leite (4) e Corrá (5) aumentaria a especificidade do diagnóstico de ventilação periódica. Por exemplo, no estudo de Ingle e colaboradores (75), a incidência de ventilação periódica cai para 20% quando ambos os critérios são utilizados em conjunto. Entretanto, fica claro, pelo previamente exposto, que alguns pacientes que também foram a óbito no período de um ano deixariam de ser identificados pela obrigatoriedade de combinação de ambos os critérios. Na verdade, os primeiros relatos sobre ventilação periódica no exercício (2, 67) não utilizavam critérios específicos para identificação do fenômeno, mas sim a constatação visual da presença de oscilações ventilatórias bem marcadas ao longo do teste cardiopulmonar de exercício. Kremser e colaboradores (67)

classificou pacientes com insuficiência cardíaca em “osciladores”, “osciladores intermediários” e “não-osciladores”, de acordo com seu comportamento ventilatório durante o teste cardiopulmonar de exercício e concluíram que a hiperventilação oscilatória correlacionava-se com a gravidade da insuficiência cardíaca. Assim, acreditamos que a avaliação quantitativa das oscilações ventilatórias durante exercício apresenta-se como alternativa ao preenchimento dicotômico (sim ou não) de critérios que foram arbitrariamente definidos (85).

Neste sentido, Francis e colaboradores (86) propuseram quantificar a ventilação periódica como a razão entre a amplitude e a média de valores de cada ciclo de ventilação periódica. Apesar de ser útil, este método torna obrigatória a identificação de ciclos definidos de ventilação periódica, sendo impossível utilizá-lo em pacientes com oscilações menos marcadas ao longo do exame. Dall´Ago e colaboradores (87) propuseram uma modificação deste método e sugeriram a quantificação das oscilações ventilatórias através da razão entre amplitude e média de valores ventilatórios a cada 20 segundos durante o teste cardiopulmonar de exercício, não sendo necessária a identificação de ciclos de ventilação periódica para realização do cálculo.

Seguindo a mesma linha de pensamento, nossa proposta nesta tese foi explorar técnicas estabelecidas para análise de variabilidade de sinais (métodos lineares, estatísticos, para análise da variabilidade no domínio do tempo e análise dos componentes principais) para quantificar as oscilações ventilatórias que ocorrem durante o teste cardiopulmonar de exercício. Não repetiremos aqui a discussão específica de cada subprojeto apresentado na sessão artigos. Faremos a partir de agora uma abordagem mais ampla, visando discutir de forma integrada dos resultados dos subprojetos.

A proposta de novos métodos ou, mais especificamente, a proposição de novas utilidades para métodos já estabelecidos em fisiologia requer a descrição do comportamento normal, fisiológico, das variáveis em estudo. Propusemos a quantificação das oscilações ventilatórias durante o teste cardiopulmonar de exercício com vistas à sua utilização na avaliação de pacientes com insuficiência cardíaca. Entretanto, nos deparamos com a inexistência de estudos que descrevessem os limites fisiológicos destas oscilações em indivíduos sadios. Qual seria a influência do tipo de exercício realizado sobre as oscilações ventilatórias? Atletas e sedentários apresentariam padrões oscilatórios semelhantes? Ocorreria

adaptação desta variável após treinamento físico? Todas estas perguntas foram aos poucos sendo respondidas pelos subprojetos aqui apresentados.

Para que pudéssemos realizar investigação a respeito das influências do tipo de exercício sobre as oscilações ventilatórias, tivemos que propor um protocolo para realização de teste cardiopulmonar de exercício em cicloergômetro de braço. Considerando que a fadiga local pode ser um importante fator limitante do exercício, inclusive acarretando interrupção do mesmo antes que o consumo máximo de oxigênio tenha sido alcançado (88, 89), propusemos e validamos um protocolo de rampa mais curto para realização de teste cardiopulmonar de exercício em cicloergômetro de braço (90). Este protocolo foi utilizado no estudo seguinte, que comparou a variabilidade ventilatória no domínio do tempo durante teste cardiopulmonar de exercício realizados com membros superiores e membros inferiores. Concluímos que apesar dos tempos respiratórios não serem influenciados pelo tipo de exercício realizado, a variabilidade ventilatória é maior durante a realização de exercício dinâmico com membros superiores do que com membros inferiores.

Posteriormente identificamos que a capacidade aeróbica de indivíduos sadios também influencia na variabilidade ventilatória durante o teste cardiopulmonar de exercício. Durante teste cardiopulmonar máximo em esteira ergométrica, atletas apresentaram menor variabilidade ventilatória no domínio do tempo do que sedentários. Resultados semelhantes foram encontrados quando utilizamos a técnica da análise de componentes principais. Tal análise permitiu ainda expandir o entendimento a respeito da variabilidade da ventilação-minuto nestes indivíduos. Enquanto em atletas a variabilidade do volume corrente é a principal responsável pela variabilidade da ventilação-minuto durante o exercício, em sedentários a variabilidade da freqüência respiratória apresenta-se como principal responsável por tais variações. Os estudos até aqui descritos eram transversais e não nos permitem inferir os reais efeitos do treinamento físico sobre a variabilidade ventilatória. Estudos anteriores demonstraram a redução das oscilações ventilatórias após treinamento físico na insuficiência cardíaca (87, 91). Pacientes submetidos a treinamento muscular respiratório e treinamento físico convencional obtiveram reduções ainda maiores nos índices de oscilações ventilatórias quando comparados a pacientes que realizaram apenas treinamento físico (92). Além disso, um relato de caso que também faz parte desta tese comprovou os efeitos benéficos da

reabilitação cardíaca sobre a reversão da ventilação periódica em um paciente com insuficiência cardíaca. Entretanto, os efeitos do treinamento sobre a variabilidade ventilatória em indivíduos saudáveis ainda não havia sido demonstrado. Assim, em estudo randomizado e controlado comprovamos que, mesmo indivíduos sadios apresentam redução da variabilidade ventilatória ao exercício após 12 semanas de treinamento físico.

O número de voluntários avaliados não foi suficiente para o estabelecimento de valores de normalidade das variabilidades de ventilação-minuto, freqüência respiratória e volume corrente no domínio do tempo durante teste cardiopulmonar de exercício. Isso foge ao escopo da tese. Entretanto, acreditamos que os estudos até aqui descritos foram suficientes para estabelecer a utilidade do método na avaliação da variabilidade ventilatória durante o exercício, além de comprovar que a variabilidade ventilatória pode ser incluída como mais uma variável fisiológica capaz de se adaptar ao treinamento físico.

No que diz respeito à aplicabilidade clínica da análise da variabilidade ventilatória no domínio do tempo, comprovamos que a mesma correlaciona-se inversamente com a fração de ejeção ventricular esquerda de pacientes com insuficiência cardíaca.

5 **CONCLUSÃO**

Concluímos que um protocolo de rampa curto durante teste cardiopulmonar de exercício em cicloergômetro de braço permitiu alcançar o mesmo consumo de oxigênio de pico, com maior carga quando comparado ao protocolo mais prolongado. O protocolo curto teve boa reprodutibilidade quando o teste cardiopulmonar de exercício foi repetido 60-90 dias após o primeiro exame em indivíduos sadios. A utilidade deste protocolo durante avaliação de outras populações deverá ser avaliada.

A variabilidade ventilatória no domínio do tempo é maior quando indivíduos saudáveis realizam teste cardiopulmonar de exercício com membros superiores do que com membros inferiores.

Em atletas a variabilidade do volume corrente é o principal componente da variabilidade do volume-minuto durante exercício. Por outro lado, em sedentários o principal componente da variabilidade do volume-minuto é a variabilidade da freqüência cardíaca. A variabilidade ventilatória no domínio do tempo é maior em sedentários do que atletas durante teste máximo de exercício.

Quando indivíduos saudáveis e sedentários foram submetidos a 12 semanas de treinamento físico houve redução da variabilidade ventilatória no domínio do tempo em indivíduos saudáveis. Houve reversão da ventilação periódica em paciente com insuficiência cardíaca submetido a programa de reabilitação cardíaca.

Em pacientes com insuficiência cardíaca a fração de ejeção correlaciona-se inversamente com a variabilidade da freqüência cardíaca no domínio do tempo.

Estudos futuros deverão analisar o poder prognóstico da variabilidade ventilatória nestes pacientes.

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